ADVISORY COMMITTEE MEETING

TOFACITINIB FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

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BRIEFING DOCUMENT

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Anti-CCP	anti-cyclic citrullinated peptide
ACE	Angiotensin-converting enzyme
ACR	American College of Rheumatology
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency of Medicines)
AFB	Acid-fast bacilli
AFSSAPS	Agence Francaise de Securite Sanitaire des Produits de Sante (French Health Products Safety Agency)
AIA	Adjuvant induced arthritis model
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BA	Bioavailability
BE	Bioequivalence
BfARM	Bundesinstitut für Arzneimittel und Medizinprodukte (German: Federal Institute for Drugs and Medical Devices)
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CD4 cells	Helper T cells
CD8 cells	Cytotoxic T cells
CFB	Change from baseline
CHF	Congestive heart failure
CI	Confidence interval
CIA	Collagen-induced arthritis model
CIOMS	Council for International Organization of Medical Sciences
CK	Creatine kinase
CLt	Total clearance
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CORRONA	Consortium of Rheumatology Researchers of North America
COX	Cyclooxygenase
CP5	tofacitinib 5 mg BID
CP10	tofacitinib 10 mg BID
CrI	Credible intervals
CRP	C-reactive protein
CsA	Cyclosporine A
CSF	Cerebrospinal fluid
CSR	Clinical study report
CT	Computed tomography
CTA	Clinical Trial Application
CTD	Common Technical Document
CV	Cardiovascular
CV-SEAC	Cardiovascular Safety Endpoint Adjudication Committee

CYP3A4	Cytochrome P450 enzyme 3A4
CYP2C19	Cytochrome P450 enzyme 2C19
CYP450	Cytochrome P450
DAS28-4(ESR)	Disease activity score defined using 28 joint counts and erythrocyte sedimentation rate
DB	Double-blind
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DMARD	Disease modifying antirheumatic drug
DBP	Diastolic blood pressure
DSMB	Data Safety Monitoring Board
E-AER	Exposure-adjusted event rate
EBER	Epstien Barr encoded ribonucleic acid
EBNA	Epstein Barr nuclear antigen
EBV	Epstein-Barr virus
EC_{50}	Concentration producing 50% of maximum effect
ECG	Electrocardiogram
eDISH	Evaluation of Drug Induced Serious Hepatotoxicity
EMA	European Medicines Agency
EOT	End of treatment
EPOCH	Etoposide-prednisone-vincristine-cyclophosphamide
ERPF	Effective renal plasma flow
ESRD	End stage renal disease
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy – Fatigue scale
FDA	Food and Drug Administration
GBM	Glomerular basement membrane
GCP	Good clinical practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HAQ-DI	Health Assessment Questionnaire-Disability Index
HDL-c	High density lipoprotein cholesterol
HLGT	High level group term
HLT	High level term
hOCT2	Human organic cationic transporter 2
HR	Hazard ratio
IC_{50}	Concentration producing 50% of inhibitory effect
ICH	International Committee on Harmonisation
ID	Identification number
IFN	Interferon
IgG	Immunoglobulin G
IL	Interleukin
ILD	Interstitial lung disease
INN	International Non-proprietary Name
IND	Investigational new drug
INR	International normalized ratio
IR	Immediate release or Incidence rate
IV	Intravenous
JAK	Janus kinase
JNC7	Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 7th Report
LCV	Lymphocryptovirus
LDH	Lactate dehydrogenase
LDL-c	Low density lipoprotein cholesterol

LOV	Last observed visit
LPD	Lymphoproliferative disorder
LTE	Long-term extension studies
MACE	Major adverse cardiovascular events
MALT	Mucosa-associated lymphoid tissue
MCavg	Time-averaged average concentration
MCID	Minimum clinically important difference
MCmax	Time-averaged maximum concentration
MCmin	Time-averaged minimum concentration
MCR	Mental Component Score
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MOA	Mechanism of Action
MPA-TLV	Sweden Medical Products Agency- Tandvårds- och läkemedelsförmånsverket
MRI	Magnetic resonance imaging
MSCT	Multislice computed tomography
mTSS	Modified total Sharp score
MTX	Methotrexate
NK	Natural killer
NDA	New drug application
NMSC	Non-melanoma skin cancer
NOEL	No observed effect level
NRI	Non-responder imputation
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
OCT	Organic cation transport
OGYI	Országos GNyógyszerészeti Intézet (National Institute of Pharmacy-Hungary)
OL	Open label
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
ONDQA	Office of New Drug Quality Assessment
OPC	Oral powder for constitution
OR	Odds ratio
OTIS	Organization of Teratology Information Specialists
P2MONO	Phase 2 studies with tofacitinib as monotherapy
P2MTX	Phase 2 studies with background methotrexate
P3DMARD	Phase 3 studies with background disease modifying antirheumatic drugs
P3MONO	Phase 3 studies with tofacitinib as monotherapy
P3MTX	Phase 3 studies with background methotrexate
PAH	Para-aminohippuric acid
PCS	Physical Component Score
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PI	Principal investigator
PID	Patient identification number
PK	Pharmacokinetic
PMAR	Population modeling analysis report
PML	Progressive multifocal leukoencephalopathy
PT	Preferred term
PTE	Probability of achieving a clinically meaningful target effect
PTLD	Posttransplant lymphoproliferative disease
PVAN	Polyomavirus-associated nephropathy
PYO	Patient years of observation
QbD	Quality by design
QD	Once daily
q2w	Once every 2 weeks
RA	Rheumatoid arthritis

RBC	Red blood cell
RCT	Randomized clinical trial
REMS	Risk evaluation and mitigation strategy
RMP	Risk management plan
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SCID	Severe combined immunodeficiency
SCLC	Small cell lung cancer
SCr	Serum creatinine
SEER	Surveillance Epidemiology and End Result
SIR	Standardized incidence ratio
SMQ	Standardized MedDRA query
SOC	System Organ Class
TB	Tuberculosis
TID	Three times per day
TNF	Tumor necrosis factor
TNFi	Tumor necrosis factor inhibitor
TyK	Tyrosine kinase
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
US	United States
USAN	United States adopted name
UTI	Urinary tract infection
VAS	Visual analog scale
WBC	White blood cell
WHO	World Health Organization
YLD	Years lived with disabilities

1. EXECUTIVE SUMMARY

Rheumatoid arthritis (RA) is a lifelong systemic autoimmune disease that afflicts roughly 1.3 million Americans and 23.7 million people worldwide and is characterized by inflammation, pain, diminished quality of life and irreversible joint destruction leading to progressive disability and significant morbidity. Patients with RA experience multiple comorbidities including diabetes, high cholesterol, and hypertension. In addition, some comorbidities may be associated with disease activity and/or treatment of RA, including increased rate of cardiovascular disease, lymphoma, and infections. Because RA is currently incurable, the goals of treatment are to reduce disease activity, improve physical function and health-related quality of life and inhibit progression of structural damage throughout the course of the patient's disease. Treatment is primarily focused on disease modifying anti-rheumatic drugs (DMARDs), which are either orally administered small molecules (e.g. methotrexate or leflunomide) or newer, injectable or intravenously-administered biologics. Although multiple DMARDs are available to treat RA, and combination therapy is frequently employed, many patients remain inadequately treated and continue to suffer pain, disability and progressive joint damage. Specifically, up to 1/3 of patients do not adequately respond and about half stop responding to any particular DMARD within 5 years (Maradit-Kremers, 2006; Duclos, 2006). Due to the duration and chronic nature of this disease, patients can expect to require treatment for up to 40 years over their lifetime. The relatively high likelihood that a patient will stop responding to any particular therapy means that many patients will exhaust available treatment options during the course of their disease. Thus, there remains an unmet medical need for additional therapeutic options with unique mechanisms of action, proven efficacy and acceptable safety profiles in patients with moderately to severely active rheumatoid arthritis.

All drugs approved for the treatment of RA over the past decade have been injectable biologic agents that primarily target extracellular cytokines. The need for a small molecule that can be administered orally and meets the criteria just described is also clearly recognized.

Towards this objective, tofacitinib was developed as a novel, oral, small molecule inhibitor of the Janus kinase (JAK) pathways that are central to the maintenance of the inflammatory state in RA. Tofacitinib is highly specific for the JAK family of kinases over the other kinases. By inhibiting the activity of JAKs, tofacitinib reduces the production of and modulates the effects of the key pro-inflammatory cytokines whose dysregulation is integral to the pathology of RA. Inhibition of JAKs leads to immunomodulation, which can be potentially linked to an increased risk of infections, and also may interfere with hematopoeisis, as has been observed with other DMARDs. The development program and proposed risk management plan were devised and undertaken with these elements of risk evaluation and mitigation in mind.

Following oral administration, tofacitinib is well absorbed, with an absolute oral bioavailability of 74%. It can be administered without regard to food. It has a half-life of approximately 3 hours and exhibits predictable, dose proportional pharmacokinetics (PK). The pharmacological activity is primarily derived from the parent molecule. The duration of

pharmacological activity is longer compared to its PK half-life, thereby supporting twice-daily dosing. Tofacitinib exhibits moderate PK variability in RA patients, with no major differences in average systemic exposure with respect to age, body weight, gender or race. The clearance pathways of tofacitinib (hepatic metabolism via cytochrome P450 (CYP)3A4 and CYP2C19 and renal clearance of parent molecule) are well characterized to allow appropriate clinical use, such as in the presence of certain concomitant medications or in patients with impaired hepatic or renal function. Tofacitinib has a low potential for impacting the PK of other drugs used in patients with RA that are metabolized by the CYP system or eliminated by the kidneys.

Development Program

The RA development program was designed to reflect prescribing practices of rheumatologists and specialists treating RA. Rheumatologists commonly initiate therapy with a non-biologic DMARD, usually methotrexate. If, after a trial period, oral DMARD monotherapy is insufficient, as it is in approximately 70% of patients (Aletaha, 2002), additional therapy is administered. Therapeutic decision making is empirical because there are no reliable means to predict which patient will respond to a given therapy or to predict the rate and extent of progression of structural damage in the individual patient.

Thus, the tofacitinib RA development program investigated its use in patients who had a previous inadequate response to DMARDs. Tofacitinib was administered either in combination with nonbiologic DMARDs (mostly methotrexate) or as monotherapy (following washout of other nonbiologic DMARDs). Tofacitinib was also investigated in patients who had a previous inadequate response to biologic DMARDs, usually a tumor necrosis factor (TNF) inhibitor.

The development program was large, robust and global in scope, with patients participating from the US, Europe, Latin America and Asia. Safety and tolerability were assessed in a demographically diverse RA patient population, reflecting those who would likely receive tofacitinib after approval. It consisted of:

- 21 completed Phase 1 studies evaluating pharmacokinetics and pharmacodynamics,
- 8 Phase 2 studies (6 completed, 2 ongoing) , all placebo controlled
    - 2 methotrexate-background dose-finding (global Study 1025, n=507; Japan Study 1039, n=136)
    - 3 monotherapy dose-finding (global Studies 1019 (n=264) and 1035 (n=384); Japan Study 1040, n=317). Study 1035 included an adalimumab monotherapy active control arm
    - 3 special topic studies (atorvastatin effect study 1109, synovial biopsy (ongoing) study 1073, MRI (ongoing) study 1068)
- 6 Phase 3 studies (4 completed, all placebo controlled; 1 ongoing, placebo controlled; 1 ongoing, MTX controlled),

- 12-month, various background non-biologic DMARDs (Study 1046/Sync, n=792)
- 12-month, methotrexate background, adalimumab active control (Study 1064/Standard, n=717)
- 24-month, methotrexate background, x-ray evaluation of joint damage (Study 1044/Scan, ongoing, with 1-year data reported, n=800)
- 6-month, methotrexate background, TNF inadequate responders (Study 1032/Step, n=399)
- 6-month, monotherapy (Study 1045/Solo, n=610)
- 24-month, monotherapy, methotrexate naïve, methotrexate active control, x-ray evaluation of joint damage (Study 1069/Start, ongoing with 1-year data not reported, n=958)

- 2 ongoing, open-label, long term extension (LTE) studies (global Study 1024/Sequel, and Japan Study 1041, n=3088 and 427, respectively, as of 29 September 2011)

Note, all study numbers start with A392, which is omitted here and only the last four digits of study numbers are used in this summary.

As of the 29 September 2011 data cutoff used for the 4-month Safety Update, the RA Phase 2, 3 and LTE studies included approximately 4800 patients across all treatment groups with nearly 7000 patient-years of tofacitinib exposure at the proposed doses of 5 mg and 10 mg twice daily (BID).

Patients treated with tofacitinib 5 mg BID, 10 mg BID, or placebo in the Phase 2 and 3 studies were predominantly from the US (20%), Europe/Canada (34%) and Latin America (15%); the remainder were mostly from Asia. The patients were 18 to 86 years of age (mean age 50-56 years, 15% ≥65 years), and the majority were women (80-87%) with long-standing RA disease (mean 5.7-13 years), and high disease activity (mean baseline 28-joint count disease activity score (DAS28) that includes patient-assessed global health and the erythrocyte sedimentation rate (DAS28-4(ESR)) of 5.83-6.71). The Phase 3 patients had comorbidities typical of the RA population, including hypertension (23%), diabetes mellitus (8%), and hyperlipidemia (24%). Thus, efficacy, safety and tolerability were assessed in a demographically diverse RA patient population refecting those who would likely receive tofacitinib after approval.

Efficacy

Tofacitinib was shown to consistently and significantly improve signs and symptoms of RA, physical functioning, the proportion of patients achieving a low level of disease activity, and patient reported outcomes such as fatigue, pain, and health-related quality of life. It also resulted in structural benefit as measured by the the van der Heijde modified Total Sharp Score (mTSS), an x-ray measure of joint damage. Improvement was demonstrated after as

little as 2 weeks of treatment, and sustained improvement was shown over more than 3 years of continued treatment in the open-label extension studies. Consistent efficacy was demonstrated when tofacitinib was administered in combination with a non-biologic DMARD, mostly methotrexate, in patients who had a previous inadequate response to non-biologic DMARDs or to TNF inhibitors, and when administered as monotherapy in patients with a previous inadequate response to DMARDs. Tofacitinib was consistently efficacious in all subpopulations assessed, including across categories of age, gender, race, RA disease severity and duration, prior RA treatments received, and concomitant RA treatment.

The primary outcomes analysis for the Phase 3 studies were analyzed conservatively utilizing a step-down procedure, which determined statistical significance for the primary endpoints, while protecting the rate of type I error, as shown in Figure 4. In this method, statistical significance could be claimed for a given endpoint only if the prior endpoint in the sequence showed significant superiority to placebo. The order of assessment of the primary endpoints was 1) proportion of patients achieving American College of Rheumatology (ACR) response criteria for at least 20% improvement from baseline (ACR20); 2) change in Health Assessment Questionnaire-Disability Index (HAQ-DI) assessment of physical functioning; and 3) proportion achieving DAS28-4(ESR)<2.6, an indicator of a very low level of RA disease activity, and henceforth referred to as DAS28<2.6. In the 1044/Scan study, change from baseline in mTSS, an x-ray measure of joint damage, was placed after ACR20 and before HAQ-DI in the step-down procedure.

For the 1044/Scan, 1046/Sync and 1064/Standard studies, the improvements in the disease activity and physical functioning endpoints, and inhibition of the progression in structural damage, at their primary time points, are shown in Table 1.

In the 1044/Scan study, the mean changes in mTSS translates to a 74% and 87% reduction in structural progression with 5 and 10 mg BID doses, respectively, vs placebo; this change in mTSS was significant for 10 mg tofacitinib BID but not for the 5 mg BID. Because of the step-down procedure the subsequent analyses of HAQ-DI and DAS28<2.6 could not be declared as significant for the 5 mg BID dose in the 1044/Scan study.

In the 1046/Sync and the 1064/Standard studies, the 5 and 10 mg BID tofacitinib doses were both superior to placebo for all primary endpoints. In the 1064/Standard study, the adalimumab active control arm achieved efficacy outcomes similar to tofacitinib 5 mg BID.

Clinically important secondary outcomes included ACR50, ACR70 and the proportion of patients showing no progression in mTSS (defined as ≤0.5 unit increase). These endpoints were not adjusted for multiple hypothesis testing.

- The ACR50 and ACR70 endpoints showed nominal statistical significance at the primary assessment time points for 1044/Scan, 1046/Sync, and 1064/Standard studies.

- In the 1064/Standard study, the ACR50 and ACR70 results for the adalimumab active control arm were superior to placebo but of lesser magnitude than both tofacitinib doses.

- In the 1044/Scan study, the proportion of patients with no progression of mTSS for both tofacitinib doses were superior to placebo at 6 months, and also at 12 months, in this pre-specified secondary endpoint.

Table 1. Efficacy Endpoints in 1044/Scan, 1046/Sync, and 1064/Standard Studies

EndPoint	1044/Scan			1046/Sync			1064/Standard			
	PBO	5 mg	10 mg	PBO	5 mg	10 mg	PBO	5 mg	10 mg	ADA
Primary										
ACR20 (%)	25.3	51.5	61.8	31.2	52.7	58.3	28.3	51.5	52.6	47.2
HAQ-DI†	0.15	0.40*	0.54	0.21	0.46	0.56	0.24	0.55	0.61	0.49
DAS28<2.6 (%)	1.6	7.2*	16.0	2.7	9.1	13.3	1.1	6.2	12.5	6.7
Mean ΔmTSS	0.47	0.12§	0.06	NA	NA	NA	NA	NA	NA	NA
Secondary										
ACR50 (%)	8.4	32.4	43.7	12.74	33.8	36.6	12.3	36.7	34.7	27.6
ACR70 (%)	1.3	14.6	22.3	3.2	13.2	16.2	1.9	19.9	21.9	9.1
No progression in mTSS (%)	77.7	88.8	86.9	NA	NA	NA	NA	NA	NA	NA

Statistically significant compared with placebo unless otherwise indicated
†Values expressed as decreases from baseline
*significance not declared due to step-down procedure
§Not statistically significant vs placebo
PBO=placebo, 5 mg=5 mg BID tofacitinib, 10 mg=10 mg BID tofacitinib, ADA =-adalimumab 40 mg SC every other week, NA=Not applicable

In the 1032/Step study, which required all participants to have previously failed to respond to at least one TNF inhibitor, and in which tofacitinib was evaluated in combination with background methotrexate, the primary outcomes were met (Table 2).

The rates and magnitudes of these improvements tended to be lower in 1032/Step than in the other background DMARD studies (1044/Scan, 1046/Sync, and 1064/Standard), which is expected for patients with biologic DMARD refractory RA.

The rates of achievement of ACR50 and ACR70 in 1032/Step were nominally significantly superior to placebo, and somewhat lower than were observed in 1044/Scan, 1046/Sync and 1064/Standard studies.

In the 1045/Solo study, which required DMARDs to be discontinued prior to study entry, tofacitinib was evaluated as DMARD monotherapy. In this study, the ACR20 and HAQ-DI endpoints were achieved, but not DAS28<2.6 (Table 2).

The rates of achievement of ACR50 and ACR70 in 1045/Solo were nominally significantly superior to placebo, and generally similar to what was observed in 1044/Scan, 1046/Sync and 1064/Standard studies.

Table 2. Efficacy Endpoints in 1032/Step and 1045/Solo Studies

EndPoint	1032/Step			1045/Solo		
	PBO	5 mg	10 mg	PBO	5 mg	10 mg
Primary						
ACR20 (%)	24.4	41.7	48.1	26.7	59.8	65.7
HAQ-DI†	0.18	0.43	0.46	0.19	0.50	0.57
DAS28<2.6 (%)	1.7	6.7	8.8	4.4	5.6§	8.7§
Secondary						
ACR50 (%)	8.4	26.5	27.8	12.5	31.1	36.8
ACR70 (%)	1.5	13.6	10.5	5.8	15.4	20.3

Statistically significant compared with placebo unless otherwise indicated
†Values expressed as decreases from baseline
PBO=placebo, 5 mg=5 mg BID tofacitinib, 10 mg=10 mg BID tofacitinib, NA=Not applicable
§Not statistically significant vs placebo

Across the Phase 3 program and across the primary and secondary outcome measures, both doses of tofacitinib were effective and the 10 mg BID dose was consistently more efficacious than the 5 mg BID dose, especially in more stringent measures such as ACR70 response rate and proportion of patients achieving DAS28<2.6. The onset of benefit was observed as early as 2 weeks and was sustained for up to 3 years.

Safety

Like other therapeutics that reduce the inflammation that underlies the disease in rheumatoid arthritis, tofacitinib has safety findings and potential risks in conjunction with its immunomodulatory mechanism. In the tofacitinib RA program this includes serious and other important infections, including tuberculosis and herpes zoster, malignancies including lymphoma, decreased neutrophil counts and neutropenia, and lipid elevations. The overall safety profile of tofacitinib, dosed at either 5 or 10 mg BID, is generally consistent with that observed in patients with moderately to severely active RA treated with biologic and nonbiologic DMARDs.

Prior to the start of studies in humans, nonclinical studies identified effects of tofacitinib on the immune and hematopoietic systems attributable to inhibition of JAKs (specifically, JAK1/3 or JAK2). These effects included:

- Dose-dependent increase in infections
- Dose dependent decrease in erythropoietic cells
- Decreases in lymphocytes and lymphocyte subsets (CD4+ cells (helper T cells), CD8+ cells (cytotoxic T cells), and natural killer (NK) cells)
- Lymphoma related to probable herpes virus reactivation in adult monkeys

These effects were generally observed at doses and exposures higher than the doses proposed for use in humans. In addition to effects on the immune and hematopoietic systems, developmental and reproductive toxicology studies identified a potential risk for women during pregnancy.

Phase 2 dose-finding studies were conducted in 1608 patients with rheumatoid arthritis; doses tested ranged from 1 mg BID to 30 mg BID administered on either a background of methotrexate or as monotherapy, for up to 6 months duration. Consistent with the nonclinical findings, the following observations were noted:

- Infections, which appeared increased at the highest doses tested; too few serious infections were observed to assess dose dependency
- Dose dependent decreases in NK cells
- Dose dependent changes in hemoglobin levels

In contrast to nonclinical findings, there were no decreases in CD4+, CD8+ and B cells in RA patients and dose-dependent decreases in neutrophils were observed.

Phase 2 studies in RA patients identified tofacitinib-related effects that were not predicted based on the nonclinical data or studies in healthy volunteers. These included:

- Dose dependent increases in total cholesterol, HDL-c, and LDL- c
- Small mean increases in serum creatinine
- Small transaminase elevations, more apparent on background methotrexate

Collectively, based on risks associated with other immunomodulatory drugs used to treat RA, the known pharmacology of tofacitinib and the Phase 2 RA data, the following safety topics were targeted for evaluation in the Phase 3 program: infections, malignancies, increased lipids and cardiovascular safety, hepatic and gastrointestinal safety and laboratory changes. In addition, safety data were monitored and evaluated for the emergence of potential new safety signals that might arise from the Phase 3 program.

Five of 6 Phase 3 controlled studies of either 6 months (2 studies) or 12 months (3 studies) duration were included in the submission and provided unblinded safety data. The long term studies, while open-label and without a control arm, are important in assessing safety with the long term use of tofacitinib and particularly for monitoring events with longer latency periods, such as malignancy and cardiovascular events.

The exposure to tofacitinib across Phase 2, Phase 3 and long term extension studies as of 29 September 2011 is provided below (Table 3). Over 3000 patients have been exposed to tofacitinib for 1 or more years, and nearly 1000 patients have been exposed for 2 or more years (Table 14).

The number of patients and patient years of observation for placebo and adalimumab were limited. Six hundred and eighty-one (681) patients were exposed to placebo in Phase 3 for a maximum of 3 to 6 months (203 patient years of exposure). Two hundred and four (204) patients were exposed to adalimumab in Phase 3 for 12 months (178 patient years of exposure).

The imbalances in numbers of patients treated, duration of treatment and patient years of exposure between placebo- or adalimumab-treated patients and tofacitinib-treated patients should be taken into consideration in comparing the safety data between treatment groups. Therefore, published data for safety events in the RA population in general and for other therapies used to treat RA patients have been presented to provide potentially useful additional context for the reviewer, particularly for uncommon or rare events.

Table 3. Numbers of Patients and Patient-Years of Exposure in Rheumatoid Arthritis Studies, Patients Receiving Tofacitinib at Any Time

Study Phase	Numbers of Patients	Patient-Years of Exposure†
Phase 2 studies	1369	419.95
Phase 3 studies	3030	2210.97
LTE* studies	3515	4409.65
Phase 2 and 3 and LTE* studies	4791	6921.91

Data as of 29 September 2011
LTE=long term extension studies.
* Patients in LTE studies were previously enrolled in a Phase 2 or 3 study and are not new patients
† Patient years of exposures in individual rows for Phase 2, Phase 3, and LTE do not match the number in the P2P3LTE row because the composite P2P3LTE number does not contain patients from 2 blinded, ongoing studies who continued participation in the LTE studies

Important safety topics are summarized below.

In the Phase 3 controlled studies (controlled period 0 to 3 months), adverse events, discontinuations due to adverse events, and serious adverse events occurred in similar proportions across all treatment groups (Table 15). The most frequently reported AEs for tofacitinib treated patients were infections, with upper respiratory tract infection and nasopharyngitis as the most frequent sites of infection. Pneumonia and herpes zoster were the most common adverse events leading to discontinuation reported for tofacitinib. Pneumonia was the most common serious adverse event reported for tofacitinib.

All-cause mortality rates within 30 days of discontinuation of study drug (adjusted for duration of exposure) were similar across treatment groups in the Phase 3 controlled studies: 0.55, 0.44, and 0.49 events/100 patient-years (pt-yrs) for tofacitinib 5 mg BID, 10 mg BID, and placebo, respectively, with all confidence intervals overlapping (Table 23).

In the long term extension studies (LTEs), there were no major differences from Phase 3 controlled studies in these general safety indicators. In the LTEs, higher incidence rates were observed for adverse events, discontinuations due to adverse events, and serious adverse events in the 10 mg BID as compared to the 5 mg BID tofacitinib group. In the Phase 3 controlled studies there was either no dose dependency or a reverse pattern (i.e. the rate or proportion was higher in 5 mg BID compared to 10 mg BID). There are important differences between controlled portions of Phase 3 and the LTE extension studies. The exposure to 10 mg dose was less than 5 mg dose in the LTE and patients on the 5 mg dose started chronologically earlier after completion of Phase 2 studies, while those on 10 mg were mainly rolled over from the Phase 3 program.

The following table summarizes safety risks that are associated with tofacitinib as well as potential risks based either on the mechanism of action of tofacitinib or observations made with other RA therapies as well as the ongoing and proposed risk mitigation activities. In addition, laboratory changes associated with tofacitinib treatment with unclear clinical significance are also shown. Detailed discussion of these and other topics are provided in the briefing document and links to the sections where these are found are provided.

Table 4. Summary of Safety Data

INFECTIONS	
Serious infections† (Section 9.7.1)	• Rates of serious infections were numerically higher with broad confidence intervals for tofacitinib treatment arms compared with placebo or adalimumab treatment arms • Serious infections occurred at a higher rate in patients ≥ 65 years of age and in patients receiving 10 mg BID in the long term studies • Serious infections generally responded to appropriate treatment • Deaths attributable to infection occurred infrequently (9 out of 206 serious infections) • Risk assessment/mitigation: LTE studies and the Consortium of Rheumatology Researchers of North America, Inc. (CORRONA) registry and other registries will be used to assess risk ratios of serious infections, herpes zoster and opportunistic infections. These risks will be communicated in the prescribing information and other communications as outlined in the Risk Evaluation and Mitigation Strategy (REMS), including that physicians should exercise caution when considering dose escalation in elderly patients, because of the increased risk of infection in these patients, particularly at the 10 mg BID dose
Herpes zoster (Section 9.7.1.3)	• Rates of herpes zoster were numerically higher for tofacitinib treatment arms compared with placebo or adalimumab treatment arms • Incidence rates were similar at the 10 mg BID compared to 5 mg BID dose • Herpes zoster rates were higher in background DMARD than monotherapy studies • Ninety three percent of cases were reported as nonserious† and most were mild or moderate in severity and resolved with conventional treatment (with or without temporary discontinuation of tofacitinib) • One event of multidermatomal herpes zoster was reported; there were no reports of visceral or central nervous system dissemination of herpes zoster • Post herpetic neuralgia was reported in < 5% of herpes zoster cases • Higher incidence of herpes zoster was associated with Asian race and longer duration of RA disease • Though not specifically studied with tofacitinib, CDC has recommended considering the use of the Zostavax vaccine in RA patients prior to the initiation of immunomodulator therapy (Centers for Disease Control, 2008).
Opportunistic infections (Section 9.7.1.4)	
Tuberculosis (Section 9.7.1.4)	• Patients were screened for latent and active tuberculosis (TB); patients with latent TB were allowed to enroll with concurrent isoniazid treatment. • No cases of TB reactivation occurred in patients who had evidence of latent TB at enrollment • There were 12 cases of TB reported; 11 cases occurred in China, India, Korea, Mexico, the Philippines and Thailand; 1 case occurred in the US 2 months after discontinuation of tofacitinib • Eight (8) out of 12 cases of TB were confined to the lung; 4 had extra-pulmonary involvement • Nine (9) out of 12 cases of TB occurred in patients receiving 10 mg BID • Risk assessment/mitigation: TB screening and appropriate treatment prior to initiation of tofacitinib treatment
Viral (Section 9.7.1.4.2)	• There were 4 reports of cytomegalovirus viremia/ infection • There was a single report of BK virus encephalopathy • Risk assessment/mitigation: Vaccine studies will evaluate the effect of

	tofacitinib on the immune response to the pneumococcal and influenza vaccines
Fungal infections (Section 9.7.1.4.2)	• Pneumocystis jirovecii pneumonia was reported in 2 patients in Japan and 1 patient in Chile • There were 2 reports of cryptococcal pneumonia and 1 report of cryptococcal meningitis • Seven (7) cases of esophageal candidiasis were reported; most were incidental findings during upper endoscopies performed for other reasons
Non-tuberculous mycobacterial infections (Section 9.7.1.4.2)	• There were 2 reports of non-tuberculous mycobacterial lung infections
MALIGNANCY	
Malignancy (Section 9.7.2)	• The standardized incidence ratio (SIR) based on comparison with the Surveillance Epidemiology and End Result (SEER) database [US General Population]) for malignancies (excluding nonmelanoma skin cancer) was 1.18 (95% CI; 0.91, 1.51). Thus, the overall rate of malignancy was consistent with the US general population. • Risk assessment/mitigation: LTE studies and the CORRONA registry and other registries will be used to assess risk ratios of malignancies including lymphoma. These risks will be communicated in the prescribing information and other communications as outlined in the REMS. Physicians are encouraged to complete all recommended screenings for malignancy prior to the initiation of tofacitinib.
Lymphoma (Section 9.7.2.1.1)	• Lymphomas occur at a higher frequency in patients with RA compared to the general population, with SIRs ranging from 2 to 5. • The SIR for tofacitinib was 2.2 (95% CI; 0.81, 4.79) • There were 6 events reported up to Jan 2012; the incidence rate across all RA studies was 0.07 events per 100 pt-yr • The types of lymphoma reported were histopathologically heterogenous and the majority were not EBV positive, consistent with lymphomas observed in the general RA population
Lung cancer (Section 9.7.2.1.2)	• Lung cancer occurs in higher frequency in patients with RA compared to the general population with SIRs ranging from 1.1 to 3.5. • The SIR for tofacitinib was 2.35 (95% CI; 1.34, 3.82). • Lung cancers reported were histopathologically heterogenous and included cases of non-small cell lung cancers and small cell lung cancers. • Thirteen (13) of 16 patients with lung cancer had significant smoking histories. • 5 patients were diagnosed within 6 months of the start of tofacitinib, suggesting that these may have been pre-existing conditions.
Breast cancer (Section 9.7.2.1.3)	• The incidence rate for breast cancer was similar to that reported in the US general population with a SIR for tofacitinib of 0.82 (95% CI; 0.41, 1.46).
Nonmelanoma skin cancer (NMSC) (Section 9.7.2.2)	• Increased risk for the development of NMSC is reported in patients with RA, as well as with the use of TNF inhibitors and prednisone. • Rate and types of NMSC observed were consistent with what is observed in the RA population. • A trend towards more NMSC was seen in patients treated with tofacitinib 10 mg BID.
BLOOD PRESSURE, LIPIDS AND CARDIOVASCULAR EVENT RATES	
Blood pressure (Section 9.7.3.1)	• There was no clinically meaningful effect of tofacitinib on systolic or diastolic blood pressure.
Lipid Increases (Section 9.7.3.2)	• Dose dependent increases in total cholesterol, LDL-c and HDL-c were observed.

	• Increases occurred within 1 to 3 months and remained stable thereafter with continued treatment with tofacitinib. • Atorvastatin at 10 mg daily effectively reduced LDL cholesterol and total cholesterol during tofacitinib therapy, but did not decrease HDL cholesterol. • While the mechanism of tofacitinib-associated lipid changes is unknown, nonclinical investigations suggest that tofacitinib reverses inflammation-mediated effects on reverse cholesterol transport. • The significance of serum lipid changes in RA patients with respect to cardiovascular risk and the interplay of these changes with inflammation are unknown. • Risk assessment/mitigation: a study of the kinetics of cholesterol flux through the HDL/reverse cholesterol transport pathway in RA patients in humans is ongoing; prescribers are instructed to assess lipid levels 4-8 weeks following initiation of tofacitinib therapy and patients should be managed according to clinical guidelines.
Cardiovascular Events (Section 9.7.3.3)	• Adjudicated event rates of myocardial infarction, stroke, congestive heart failure and a composite endpoint of major adverse cardiovascular events (MACE) were all low in the Phase 3 controlled studies and remained low in the long term extension studies. • No evidence for an increase in cardiovascular risk has been observed. • Risk assessment/mitigation: retrospective and prospective cohort analysis of cardiovascular events utilizing the CORRONA registry will be performed to assess the risk ratios of cardiovascular events.
HEPATIC AND GASTROINTESTINAL SAFETY	
Hepatic safety (Section 9.7.4)	• Potential for hepatic toxicity associated with tofacitinib use is low. • Elevations in transaminases ≥ 3 x upper limit of normal (ULN) were uncommon in the Phase 3 and long term studies and were also observed in placebo treated patients. Transaminase elevations were generally less when tofacitinib was not administered with traditional DMARDs (mostly MTX). • One case of possible drug induced liver injury (DILI) was identified; the patient recovered fully. This case was an atypical presentation for DILI, with unusual features.
Gastrointestinal Perforations (Section 9.7.5)	• Based on a thorough and systematic search of the database and subsequent clinical evaluation of potential cases, 10 events of gastrointestinal perforation were identified. • The overall incidence rate was intermediate between published rates for tocilizumab and TNF inhibitors. • There was no apparent dose response. • Nine (9) of 10 perforations occurred in the lower gastrointestinal tract. • In general, patients had a history of diverticulitis and/or concomitant treatment with nonsteroidal anti-inflammatory drugs and corticosteroids. • Risk assessment/mitigation: LTE studies and the CORRONA registry and other registries will be used to assess risk ratios of gastrointestinal perforation. The risk of GI perforation will be communicated in the prescribing information and other communications as outlined in the REMS.
LABORATORY CHANGES	
Hemoglobin (Section 9.7.6)	• Anemia was mostly mild to moderate (Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) criteria: decrease from baseline ≥1 to ≤2 g/dL) and occurred in similar proportions for tofacitinib and placebo during the controlled portion of the Phase 3 studies. • Increases in mean hemoglobin levels were observed with 5 mg BID

	tofacitinib; there was little change observed with tofacitinib 10 mg BID or placebo. • Risk assessment/mitigation: prescribing information includes guidelines for use based on hemoglobin levels. Hemoglobin should be monitored after 4-8 weeks of therapy and every 3 months thereafter.
Neutrophils (Section 9.7.7)	• Dose dependent decreases in neutrophil counts were observed in tofacitinib treated patients. • Neutrophil counts largely remained within reference ranges. • No confirmed neutrophil counts < 500 cells/mm^3 were observed. • No relationship was observed between neutropenia of any level and the development of treated or serious infections. • Risk assessment/mitigation: prescribing information includes guidelines for use based on neutrophil counts. Neutrophils should be monitored after 4-8 weeks of therapy and every 3 months thereafter.
Lymphocytes (Section 9.7.8)	• OMERACT defined confirmed lymphopenia (all categories) was similar for tofacitinib and placebo-treated patients • Mean total lymphocyte counts increased initially with tofacitinib, but increases did not persist • NK cell decreases were observed in tofacitinib-treated patients • Model-based assessment of NK cells counts did not show an association between lower NK cell counts and increased incidence of serious infections, herpes zoster or malignancies.
Creatinine (Section 9.7.9)	• Small mean increases from baseline in serum creatinine levels were seen in all treatment groups; increases in tofacitinib treated patients were estimated to be 0.02 and 0.04 mg/dL greater than placebo. • Increases occurred within 3 months and remained stable thereafter. • Individual patient creatinine levels largely remained within reference range. • There was no evidence for nephrotoxicity in healthy volunteers or RA patients. • Risk assessment/mitigation: a measured renal function study will evaluate the mechanism of serum creatinine increase in RA subjects
†Serious infections were defined as those requiring hospitalization or parenteral antimicrobial therapy	

The risks associated with tofacitinib 5 and 10 mg BID are generally similar and consistent with those of approved therapies for patients with moderate to severely active RA. Immunomodulation and immunosuppression occur over a spectrum and dose dependency of related risks is common. Based on the totality of the data, safety issues have remained consistent and predictable through all phases of development in RA patients. The proposed approaches to management of these risks will be familiar to rheumatologists currently treating RA patients. Based on comparisons with the placebo and adalimumab treatment groups within the tofacitinib clinical studies as well as published data on other RA therapies (including biologic and non-biologic DMARDs), the safety profile for tofacitinib is acceptable for both proposed doses in patients with RA. This conclusion is based on the following considerations:

- The risk profile is considered to be manageable with appropriate patient selection and screening, routine monitoring and medical management when necessary

- Proposed patient management will be familiar to rheumatologists currently treating patients with existing immunomodulatory agents used to treat RA

- Safety concerns are addressed with a risk management program that identifies pharmacovigilance and additional risk mitigation activities that will be undertaken to facilitate the safe and effective use of tofacitinib as noted in Table 4 and further discussed in Section 10.

- The Risk Evaluation and Mitigation Strategy (REMS) outlines a proposed education/communication plan for healthcare providers and patients regarding the risks associated with and proper use of tofacitinib.

Specific and detailed risk assessment/mitigation strategy will continue to be developed and finalized in collaboration with the FDA.

Summary of Benefit-Risk

The overall benefit-risk of tofacitinib is favorable in light of consistent efficacy across a wide array of measures of benefit to RA patients and a predictable and manageable adverse effect profile. Benefit-risk was assessed in the context of the benefits and risks associated with current RA therapies, the comorbidities of the disease itself and the need for additional treatment options.

Up to one-third of RA patients receiving currently approved DMARD therapies show inadequate response in this serious, chronic, progressive and disabling disease that lasts 20 to 40 years and for which there is no cure. Approximately half of the RA patients stop responding to any particular biologic or non-biologic DMARD within 5 years. All recently approved therapies for RA are injectable biologics associated with their own specific limitations and concerns, including immunogenicity and infusion or injection site reactions. Thus, there is an unmet medical need for therapeutic options with novel mechanisms of action, proven efficacy and acceptable safety profiles in patients with moderately to severely active RA.

The successful treatment of RA requires demonstration of substantial benefit across multiple domains of clinical efficacy and the inhibition of progression of joint damage. The clinical efficacy measures impacting the assessment of benefit-risk balance are broad-based and include improvements in ACR 20/50/70, DAS28-4(ESR) $\leq$3.2 and <2.6, and clinically meaningful improvements in physical function and other patient reported outcomes.

Robust efficacy was demonstrated for both the 5 mg BID and 10 mg BID doses across a broad range of endpoints and patient populations, whether dosed in combination with non-biologic DMARDS or as monotherapy. The 10 mg BID dose was consistently more efficacious than the 5 mg BID dose, especially in more stringent measures such as ACR70 response rate and proportion of patients achieving DAS28<2.6.

Safety outcomes impacting the assessment of benefit-risk balance should be viewed in the context of both the disease and current therapies. RA is associated with significant co-morbidities such as increased serious infections, certain malignancies such as lung cancer and lymphomas, CV- associated morbidity, and premature death. These important safety

events are similar for tofacitinib and approved biologic and nonbiologic DMARDs, and were the primary focus of the benefit-risk assessment for tofacitinib.

Based on the totality of data, the safety profile was similar between the 5 and 10 mg BID doses of tofacitinib during the Phase 3 studies. Safety and laboratory measures that show a dose dependency and thus a potential increased risk at the 10 mg BID dose include serious infections, tuberculosis, changes in hemoglobin, neutrophils and total cholesterol and LDL-c; a trend was observed towards more nonmelanoma skin cancers in patients treated with tofacitinib 10 mg BID.

The proposed recommendations for patient management will be familiar to rheumatologists currently treating patients with existing agents for treating RA; tofacitinib should be prescribed by health care professionals with expertise in the diagnosis and use of immunomodulatory agents in RA.

Benefit-Risk Conclusions

- The benefit-risk profile of tofacitinib is favorable for use in RA patients, as demonstrated in the large and diverse population enrolled in the clinical program.

- Tofacitinib provides an innovative oral therapeutic option and warrants approval for use in patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs.

- Pfizer is committed to ongoing pharmacovigilance to further characterize the long term safety profile of tofacitinib, risk mitigation and other risk management activities to facilitate its safe and effective use.

- The proposed indication for tofacitinib is treatment of adult patients with moderately to severely active established RA who have had an inadequate response to nonbiologic and/or biologic DMARDs. The proposed dosing is 5 mg twice daily, used as monotherapy or in combination with methotrexate (MTX) or other nonbiologic DMARDs. Some patients may benefit from an increase to 10 mg twice a day based on clinical response.

- Collectively, the efficacy and safety data and the immunomodulatory mechanism of action of tofacitinib support the selection of the lowest effective dose (5 mg BID) as the recommended dose. However, at the individual patient level, for those with an inadequate clinical response to 5 mg BID, an increase to 10 mg BID may be appropriate, based on the physician's evaluation of benefit-risk in that patient.

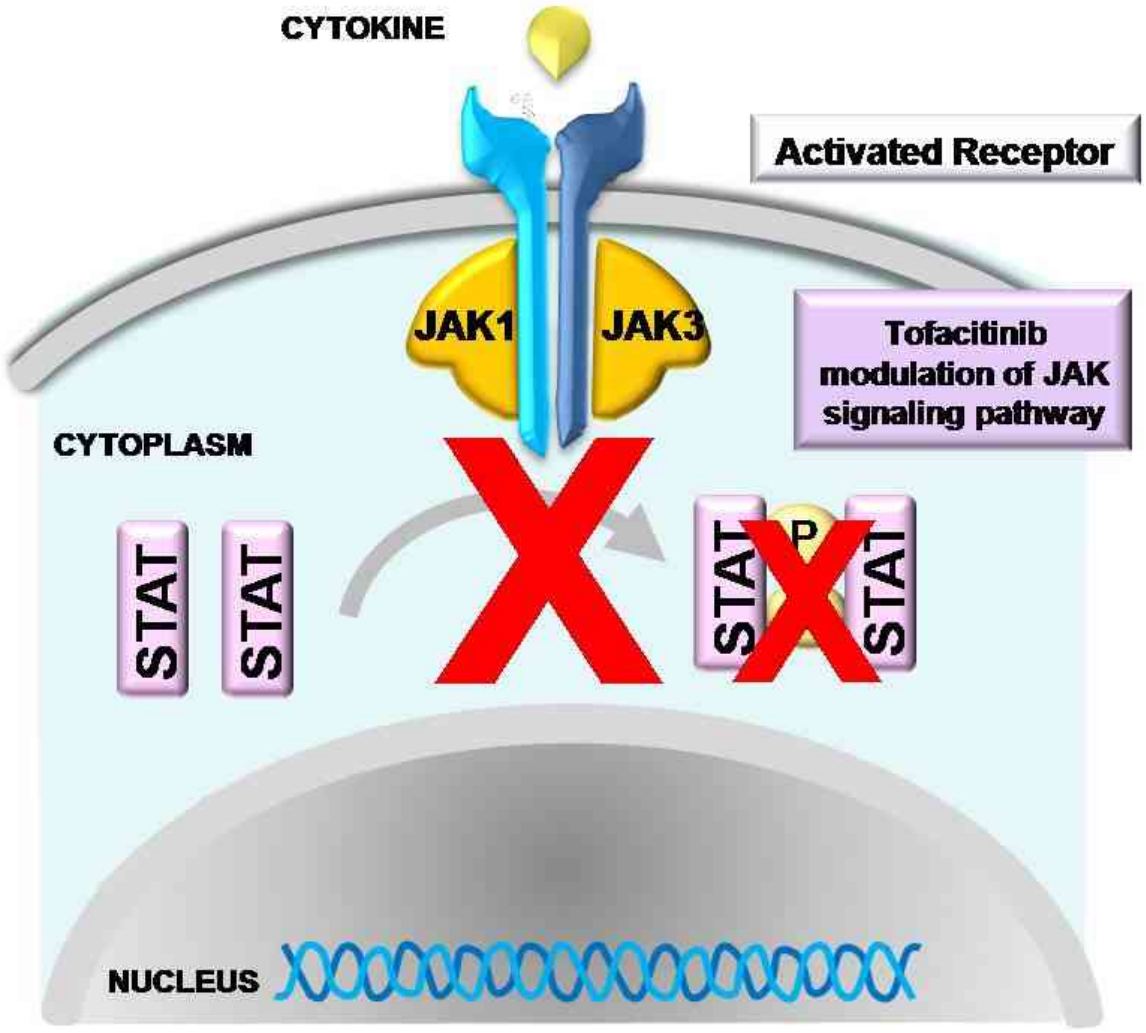
2. PRODUCT DEVELOPMENT RATIONALE

2.1. Product Description and Scientific Rationale

Tofacitinib is a potent, selective inhibitor of the JAK family of kinases with a high degree of selectivity against other kinases in the human genome. In kinase assays, tofacitinib, inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2. In cellular settings where Janus kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain containing receptors for several cytokines, including IL-2, -IL-4, IL-7, IL-9, IL-15 and IL-21. These cytokines are integral to lymphocyte activation, proliferation, and function and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and IFNγ. At higher exposures, inhibition of erythropoietin signaling could occur via inhibition of JAK2 signaling.

RA is driven by dysregulation in the immune system, leading to uncontrolled inflammation. The keys to this imbalance are the messenger proteins (cytokines) that cells use to communicate with each other. Dysregulated production of multiple cytokines plays a fundamental role in RA. All currently available biologic DMARD therapies are injectable, most of which, including tumor necrosis factor (TNF) inhibitors, target cytokine/receptor interactions. Cytokines binding to their receptors trigger inflammatory pathways inside cells and JAKs act as key hubs in these pathways, also known as JAK pathways, to control the action of multiple cytokines that cause inflammation. The JAK hubs can be targeted with small molecules, thereby enabling oral treatment. Tofacitinib is an oral therapy with a novel mechanism of action that targets multiple cytokines by leveraging the central critical importance of the JAK pathways in the pathogenesis of RA.

Figure 1. Mechanism of Action for Tofacitinib



JAK=Janus kinase; P=phosphate; STAT=signal transducer and activator of transcription.

- Tofacitinib binds in the catalytic cleft in the kinase domain of JAKs
- Tofacitinib modulates the JAK signaling pathways at the point of JAK, preventing the phosphorylation and activation of signal transducer and activators of transcription (STAT).
- Inhibition of JAK1/JAK3 is expected to block signaling through the common γc -containing cytokine receptors, including those for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21; these cytokines are integral to lymphocyte activation, proliferation and function and may thus result in modulation of multiple aspects of the immune response.
- In addition, inhibition of JAK1 may lead to some modulation of additional cytokine receptor signaling, including IFN-α, IFN-β and IL-6.

Source: Shuai, 2003

2.2. Epidemiology of Rheumatoid Arthritis

RA is a chronic systemic autoimmune disease that affects roughly 1.3 million Americans and 23.7 million people worldwide (World Health Organization (WHO) Global Burden of Disease, 2004). It is characterized by inflammation, joint destruction, and progressive disability. Joint destruction is believed to be irreversible resulting in significant cumulative morbidity.

RA affects women three times more frequently than men (Kvien, 2006; Sullivan, 2010), with typical onset of RA occurring between the ages of 20 to 40 years. The clinical consequences of RA are substantial. In addition to loss of employment, during years of typically high productivity, disability hinders the ability of patients to undertake their activities of daily living and can impact genderual and social functioning (Laas, 2008; Linde, 2008; Uhlig, 2007). WHO estimated that RA was the 31st leading cause of years lived with disabilities (YLD) globally in 2000 (Mathers, 2002), and 11.9 million people worldwide are moderately to severely disabled due to RA (WHO, 2004).

Rheumatoid arthritis is a lifelong, chronic disease and patients experience a broad range of co-morbidities. Compared with the general population, RA patients are at a higher risk for cardiovascular disease, lymphoma, lung cancer and serious infections (Michaud, 2007). These patients are also treated with multiple classes of agents, including NSAIDs, glucocorticoids, and DMARDs, each of which carry significant risks. These risks include serious and opportunistic infections, malignancies (including lymphoma), and transaminase elevations with the potential for hepatic injury (Greenburg, 2010; Sokolove, 2010; Askling, 2010). Some agents are also associated with increases in lipids, hemopoietic changes, GI events, infusion and injection site reactions and demyelinating disorders (US FDA, Drug Approval Package, Humira, 2008; Burmester, 2009; Gottlieb, 2011).

2.3. Current Treatment of Rheumatoid Arthritis and Unmet Medical Need

Current treatment options for RA attempt to control disease activity, alleviate signs and symptoms, maintain physical function, optimize quality of life, and reduce joint destruction with the goal of inducing clinical remission.

Treatment of RA is typically initiated with nonsteroidal anti-inflammatory drugs (NSAIDs) and/or low-dose glucocorticoids, with introduction of nonbiologic DMARDs (typically MTX) as quickly as possible after RA diagnosis (Smolen, 2010; Matsumoto, 2011). If MTX or other nonbiologic DMARD treatment does not adequately control the disease, a TNF inhibitor is typically added to the regimen (or offered as monotherapy if the patient cannot tolerate MTX). If an inadequate response is observed to a treatment regimen that includes a TNF inhibitor, a common response is to switch the biologic DMARD, either from one TNF inhibitor to another or to a biologic DMARD with a different mechanism of action.

Despite the availability of multiple therapeutic options, many patients fail to adequately respond to treatment or stop responding over time. There is no reliable way to predict which patients will respond to a given treatment. One third of patients are estimated to fail to respond to treatment with a TNF inhibitor (Opar, 2010). Additionally, only 30% of patients with moderate disease achieve a "Disease Activity Score (DAS) defined remission", (defined as DAS28 <2.6), falling to less than 10% after 12 months treatment with biologic DMARDs (Aletaha, 2010; Listing, 2006). This limited treatment success rate further demonstrates the need for additional therapeutic options.

Tofacitinib is an oral agent with a novel mechanism that targets a key inflammatory pathway implicated in RA, thereby providing the possibility of inducing responses in patients who have failed previous nonbiologic or biologic DMARD therapies.

3. OVERVIEW OF DEVELOPMENT PROGRAM AND EXPOSURE

3.1. Development Program

The tofacitinib RA development program was designed to investigate safety and efficacy in patients with moderately to severely active RA who have had an inadequate response to nonbiologic and/or biologic DMARDs. Four of the Phase 3 studies were designed to evaluate tofacitinib in patients who had an inadequate response to nonbiologic therapies; an additional study specifically evaluated tofacitinib in patients who had an inadequate response to a TNF-inhibitor. The tofacitinib RA development program was also designed to investigate the use of tofacitinib when administered either as monotherapy (following washout of other DMARDs) or in combination with nonbiologic DMARDs (typically MTX) to reflect the different prescribing practices which may be used for a new therapy in the treatment of RA. Adalimumab was used as the active control in two studies (one Phase 2 monotherapy study and one Phase 3 study on a background of MTX).

Endpoints evaluated in the development program included signs and symptoms of active RA, pain, physical function, fatigue and other patient reported outcomes, and assessments of disease activity including proposed targets of low disease activity (DAS ≤3.2) and (DAS <2.6). Inhibition of structural damage was also examined with tofacitinib treatment added to a stable background of MTX therapy in an ongoing 2-year study, from which 1-year data were included in the marketing application. These assessments of efficacy are valid, widely accepted and have been used in many DMARD registration programs.

3.2. Exposure and Clinical Studies

The RA tofacitinib clinical development program, as of 29 March 2011, consisted of 21 completed Phase 1 studies, 8 Phase 2 studies (6 completed, 2 ongoing), 6 Phase 3 studies (4 completed, 2 ongoing), and 2 ongoing, open-label, extension studies that were included in the marketing application (Table 5). The beginning prefix of the study numbers (A392) is omitted for brevity in this document; studies are also designated by name, when appropriate.

As of the 29 September 2011 data cut-off date used for the 4-month Safety Update, the RA Phase 2, 3 and LTE studies included approximately 4800 patients across all tofacitinib treatment groups with nearly 7000 patient-years of exposure at tofacitinib doses of 5 mg and 10 mg BID.

In the Phase 2 and 3 studies, patients were administered tofacitinib, either as monotherapy or in combination with background nonbiologic DMARDs (usually MTX), in multicenter, randomized, double-blind, placebo-controlled studies. Duration of treatment with tofacitinib in the Phase 2 and 3 studies ranged from 6 weeks to 2 years (1 year of data was available at the time of application from the ongoing 2-year study). Eligible patients were given the option to continue participation in the program by enrolling in one of two ongoing, long-term open-label extension (LTE) studies. Patients in the LTE studies have continued treatment for more than 3 years.

Table 5. Studies in the Tofacitinib Rheumatoid Arthritis Development Program Included in the Marketing Application

	Studies Included§
Phase 1 Completed Studies (pooled for safety analyses**)**	1002, 1003, 1004, 1005, 1006, 1010, 1013, 1014, 1015, 1020, 1028, 1033, 1036, 1054, 1056 , 1059, 1065, 1071, 1075, 1076, 1077
Phase 2 Completed RA Studies	
Phase 2 Monotherapy Studies∗ (pooled for safety analyses)	1019, 1035, 1040
Phase 2 Background Methotrexate Studies (pooled for safety analyses)	1025, 1039
Phase 2 Study with Atorvastatin	1109
Phase 2 Ongoing RA Studies	1068, 1073
Phase 3 Completed RA Studies	
Phase 3 Monotherapy Study	1045 (Solo study)
Phase 3 Background DMARD Studies (pooled for safety analyses)	1032 (Step study), 1044 1-yr†(Scan study), 1046 (Sync study), 1064 (Standard study)
Phase 3 Background MTX Studies (pooled for safety analyses)	1032 (Step study), 1044 1-yr†(Scan study), 1046 (Sync study; using background MTX pts only), 1064 (Standard study)
Phase 3 Ongoing RA Studies	1069 (Start study‡), 1044 (Scan study†)
Ongoing Long Term Extension Studies (pooled for safety analyses)	1024 (Sequel study), 1041*

DMARD = disease modifying antirheumatic drug; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drug; RA = rheumatoid arthritis
∗ No background DMARD; NSAID, prednisone, and anti-malarial use allowed
† Study will be ongoing at time of submission and data from a planned 1-year Analysis is included. The 1-year Analysis is available in Module 5
‡ Limited safety data will be provided from the ongoing, blinded study A3921069 (SAEs, deaths, discontinuations due to AEs and AEs of special interest).
§ The beginning prefix of the study numbers (A392) is omitted for brevity in this table

4. PROPOSED INDICATION AND DOSAGE AND ADMINISTRATION

The proposed indication for tofacitinib is for the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs.

The recommended starting dose of tofacitinib is 5 mg administered twice daily. Some patients may benefit from an increase to 10 mg administered twice daily, based on clinical response. Tofacitinib may be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs.

5. REGULATORY HISTORY

Pfizer has had ongoing interactions with the FDA throughout the development program of tofacitinib for treatment of rheumatoid arthritis (RA). The IND for tofacitinib in this indication was originally submitted in October 2004. In January 2007, at the end of Phase 2A, the Division of Analgesia, Anesthesia and Rheumatology Drug Products (DAARP), provided feedback on the Phase 2B program to support selection of doses for Phase 3.

In December 2008 Pfizer participated in an End of Phase 2 meeting with the Division where input was received regarding the proposed Phase 3 development program for tofacitinib. The Agency and Pfizer reached agreement on the Phase 3 program including the non-clinical program and the proposed Phase 3 clinical development plan, including the dose selection rationale, study designs and the analysis of clinical study endpoints. Agreement was also reached on the size of the safety database needed to support registration.

In February 2011, a pre-NDA meeting was held with the Division of Pulmonary, Allergy and Rheumatology Products (DPARP); agreement was reached on the content and format of the RA New Drug Application.

A pre-submission meeting for the NDA was also held with the Office of New Drug Quality Assessment (ONDQA) in March 2011 to discuss the Chemistry, Manufacturing and Control component of the NDA.

Pfizer submitted a New Drug Application (NDA) in October 2011.

A 120-Day Safety Update was submitted in February 2012 in compliance with the regulatory requirements.

6. NONCLINICAL PHARMACOLOGY, PHARMACOKINETICS, AND TOXICOLOGY

The comprehensive nonclinical program for this small molecule consisted of toxicology studies in rodents of up to 2 years in duration and nonhuman primates for up to39 weeks duration. This nonclinical program differs from those conducted for biologic DMARDs where long term rodent toxicology studies are usually not possible for a number of reasons such as immunogenicity and target specificity.

6.1. Nonclinical Pharmacology

The JAK family of tyrosine kinases mediates signal transduction from type I and II cytokine receptors critical for leukocyte activation, proliferation, survival and function. JAK inhibition results in the suppression of immune and inflammatory responses through simultaneous blockade of the signaling of multiple cytokines.

Tofacitinib is a potent inhibitor of the JAK kinase family, with a high degree of selectivity within the human kinome (Karaman et al, 2008). While tofacitinib shows nanomolar inhibitory potency against all JAK family kinases in enzyme studies, it shows functional specificity for JAK1 and JAK1/3 over JAK2 in cell assays. In whole blood, γc cytokine dependent activation (driven by JAK1/3) was potently inhibited by tofacitinib, with functional selectivity over GM-CSF-dependent (JAK2-driven) activation of the pathway. Tofacitinib is efficacious in rodent models of arthritis as assessed by clinical and histological measures of disease progression in the mouse collagen-induced arthritis (CIA) model and rat adjuvant induced arthritis (AIA) model. At the efficacious doses, significant reduction in inflammatory proteins and gene sets were also observed in the mouse and rat.

There were no noteworthy effects on serum cholesterol or triglycerides in repeat-dose toxicology studies in healthy rats and cynomolgus monkeys dosed with tofacitinib. To understand the effects of tofacitinib on cholesterol in patients, investigative studies were conducted with tofacitinib in the rat AIA model.

Collectively, these data suggest that development of AIA in rats impairs the reverse cholesterol transport (RCT) process resulting in a decrease in the rate of esterification of plasma cholesterol and a decrease in total plasma cholesterol. Treatment of diseased AIA rats with tofacitinib at doses which had previously been shown to decrease the level of acute phase proteins, inflammatory mediators and disease severity restores the rate of RCT to levels observed in non-diseased naïve rats. The increase in RCT is consistent with the increase in fecal excretion of cholesterol as bile acids and neutral sterols and the decrease in lipid levels in macrophages which was also noted in tofacitinib treated animals. Because RCT is a pathway by which accumulated cholesterol is transported from the vessel wall to the liver for excretion (Ohashi, 2005), the nonclinical mechanistic data showing that tofacitinib increased RCT via increased ApoA1 and lecithin cholesterol acyltransferase activity supports the prospect that this mechanism is not proatherogenic.

6.2. Pharmacokinetics

The absorption, distribution, metabolism, and excretion (ADME) of tofacitinib was evaluated in a number of nonclinical studies to support its clinical development. In support of pharmacokinetic and safety testing, the majority of ADME characterization was performed in rats and monkeys. In early nonclinical studies to predict human pharmacokinetics, dogs were included to support allometric scaling assessments.

Following oral administration to rats, dogs, and monkeys, tofacitinib showed rapid absorption and elimination. Oral bioavailability was moderate to good in the three species tested. Systemic exposure (peak concentration (C_{max})and area under the concentration-time curve (AUC)) to tofacitinib increased with increasing dose in rats (up to 100 mg/kg/day) and monkeys (up to 50 mg/kg/day). Tofacitinib had low to moderate protein binding in the plasma of all species (nonclinical and human). Given the species differences in plasma protein binding, exposure margins were calculated using unbound concentrations. All human metabolites are less than 10% of circulating parent and are represented in nonclinical species. Clearance pathways and metabolic and transporter drug-drug interaction (DDI) profiling are well understood. Additional data supporting the ADME and PK/PD characterization of tofacitinib in humans are discussed in Section 7, Clinical Pharmacology.

6.3. Toxicology

Immune and hematopoietic organ systems were identified as targets in repeat-dose toxicity studies. Effects on the immune system (including decreased circulating lymphocytes, lymphoid depletion of lymph nodes, spleen, thymus and bone marrow, and bacterial and viral infections) were consistent with inhibition of JAK1/3. Decreases in hemoglobin, hematocrit, erythrocyte numbers and reticulocytes were attributed to JAK2 inhibition. These effects were generally reversible during a 4-week recovery phase in the 4- and 6-week monkey and rat studies, respectively. Doses of tofacitinib at 1 and 10 mg/kg/day in rats (approximately, 0.4/1 and 5/11 –fold for males and females compared to the unbound area under the concentration curve (AUC) of the 10 mg BID dose) and 2 mg/kg/day (approximately 0.6-fold compared to the unbound AUC of the 10 mg BID dose in adult cynomolgus monkeys were tolerated in studies up to 6 months and 39 weeks duration, respectively. In the 39-week juvenile monkey study, the T-dependent antibody response to antigen immunization was decreased at the high dose of 10 mg/kg/day (approximately 2.5-fold exposure multiple compared to the unbound AUC of the 10 mg BID dose).

In the adult 39-week monkey study, lymphomas were observed in 1 male and 2 females at the high dose of 10 mg/kg/day (approximately 3-fold exposure multiple compared to the unbound AUC of the 10 mg BID dose). In adult monkeys, the two B cell lymphomas were positive for the presence of lymphocryptovirus (LCV), a genus of gamma herpes viruses similar to the human Epstein-Barr virus (Carveille, 2008). These lymphomas are considered secondary to over-immunosuppression and viral transformation (McInnes, 2002; Schmidtko, 2002; Swerdlow, 2008). The third lymphoma was comprised of T cells, but due to its small size and lack of adequate tissue it could not be further characterized. Follicular lymphocyte hyperplasia was observed at all dose levels in the 39-week monkey study. Based on the morphology, which resembled normal reactive follicular lymphoid hyperplasia, and the lack

of staining for LCV, this lymphocyte hyperplasia is not considered a precursor of lymphomas. Simple reactive follicular lymphoid hyperplasia is a normal response that is not considered adverse or a concern for human health (Greaves, 2007). At the same doses and exposure levels, lymphoma and follicular lymphocyte hyperplasia were not observed in a 39-week juvenile monkey study.

Tofacitinib is not mutagenic or genotoxic based on a series of in vitro and in vivo tests for gene mutations, chromosomal damage, and DNA damage.

No treatment-related tumors were observed in the 6-month rasH2 transgenic mouse study up to the high dose of 200 mg/kg/day (approximately 19-fold compared to the unbound AUC of the 10 mg BID human dose). In the 2-year rat carcinogenicity study, tofacitinib treatment-related neoplastic findings included: benign Leydig cell tumors at ≥30 mg/kg/day (approximately 17-fold compared to the unbound AUC of the 10 mg BID human dose) and benign angiomas at 10 mg/kg/day (approximately 5-fold compared to the unbound AUC of the 10 mg BID human dose) in males; malignant hibernomas (tumors of brown adipose tissue) at ≥30 mg/kg/day (approximately 41-fold compared to the unbound AUC of the 10 mg BID human dose), and benign thymomas in females at 100/75 mg/kg/day (approximately 94-fold compared to the unbound AUC of the 10 mg BID human dose) in females.

Based on in vitro mechanistic studies, the testicular Leydig cell tumors are attributed to inhibition of prolactin (PRL) signaling via JAK2 within Leydig cells which causes a decrease in Leydig cell luteinizing hormone (LH) receptor number and thus a decrease in testosterone production with a concomitant increase in circulating LH to maintain testosterone levels. This mechanism is analogous to that of agents which induce Leydig cell tumors in rats secondary to decreasing circulating PRL levels, a mechanism not considered relevant to humans (Prentice, 1992). The weight of evidence from the number of rat studies with Leydig cell tumors, without observing similar effects in human Leydig cells, suggest that human Leydig cells are quantitatively less sensitive than rats in their proliferative response to LH (Prentice, 1995; Clegg, 1997; Cook, 1999; Silva-Lima, 2000). Hibernoma incidence at 10 mg/kg/day did not differ significantly from that in the control group, was within the recent historical spontaneous incidence, and is, thus, considered the no observed effect level (NOEL). Increased hibernoma incidence was associated with exposure margins of approximately 11-fold at the NOEL, and approximately 41-fold at the lowest observed effect level (LOEL). Hibernomas in humans, unlike rats, are extremely rare, uniformly benign, and typically occur at peripheral subcutaneous sites amenable to detection and excision (Baldi, 2004; Moretti, 2010). Based on these characteristics, the margins from the rat carcinogenicity study do not imply a significant human risk for hibernoma at clinical exposures. Increased incidence of benign thymoma was statistically significant only in high dose female rats (100/75 mg/kg/day). Based on the high exposure margin (approximatley 41-fold at the NOEL, and approximately 94-fold at the LOEL) compared to clinical exposure to tofacitinib, the risk to humans is considered low. Based on a lack of dose-response, increased incidence in a single sex, and a single species, the marginally increased incidence of benign angioma in low dose male rats (10 mg/kg/day) is not considered biologically meaningful and does not pose a relevant risk for humans treated with tofacitinib.

Tofacitinib had no effect on fertility of male rats, but in treated female rats tofacitinib decreased pregnancy rate, numbers of corpora lutea, implantation sites, and viable fetuses, with an increase in early resorptions. Tofacitinib was teratogenic (visceral and skeletal abnormalities) in rats and rabbits. In the peri/postnatal development study in rats, tofacitinib decreased the number of delivered and live born pups, and reduced pup survival. Treatment-related effects on reproduction or development occurred at exposures approximately ≥6-fold compared to the unbound AUC at the 10 mg BID human dose.

6.4. Nonclinical Conclusions

Tofacitinib is a potent inhibitor of the JAK family, with a high degree of selectivity over other kinases, and moderate functional selectivity for inhibition of JAK1 and JAK3 over JAK2. Efficacy in animal models of arthritis is attributed to inhibition of JAK1/3 and to a lesser extent JAK1/2, which interrupts the intracellular signaling of several cytokines that modulate multiple aspects of the immune response.

Adverse effects of tofacitinib on the immune and hematopoietic systems in repeat-dose nonclinical toxicity studies are attributable to inhibition of JAK1/3 or JAK2. Tofacitinib is not genotoxic. No treatment-related neoplasia was observed in rasH2 transgenic mice. Treatment-related tumors observed in the rat carcinogenicity study are considered to be not relevant or of low relevance to humans based on mechanism or exposure margins. Based on the results from developmental and reproductive toxicology studies, tofacitinib should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus; women should not breastfeed while being treated with tofacitinib.

Collectively, the nonclinical data support the chronic use of tofacitinib for the treatment of rheumatoid arthritis.

7. CLINICAL PHARMACOLOGY

The clinical pharmacology of tofacitinib has been characterized based on 13 in vitro and 21 Phase 1 studies along with 5 Phase 2 dose-finding studies providing population PK and dose response information.

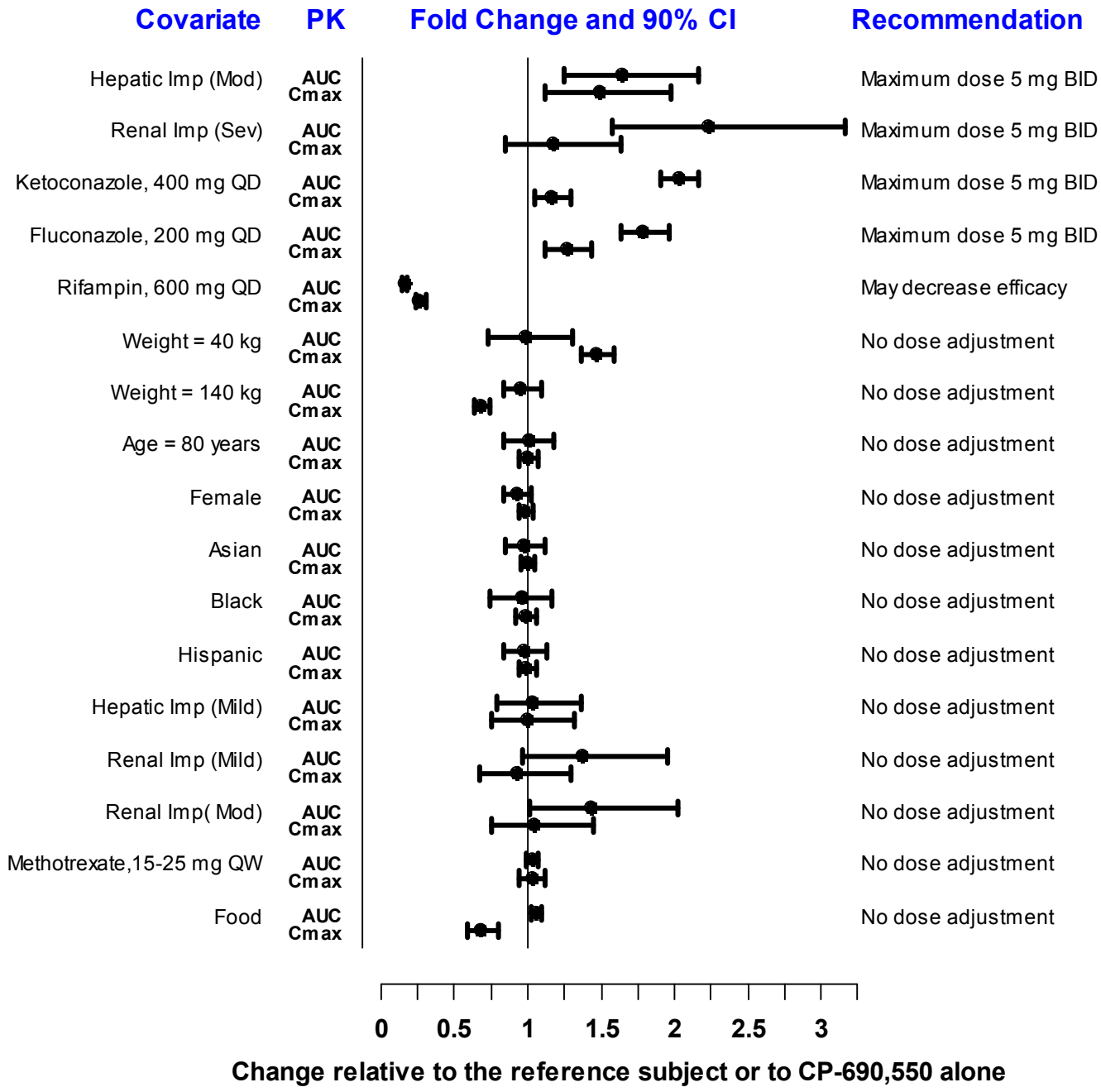
The PK profile of tofacitinib is characterized by rapid absorption (peak plasma concentrations are reached within 0.5-1 hour), rapid elimination (half-life of ~3 hours) and dose proportional increases in systemic exposure. Steady state concentrations are achieved in 24 to 48 hours with minimal accumulation after BID administration.

Tofacitinib is well absorbed, with an oral absolute bioavailability of 74%. It has a plasma protein binding of 39%. Clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. The metabolism is primarily mediated by CYP3A4 with minor contribution from CYP2C19. The pharmacologic activity of tofacitinib is primarily attributed to the parent molecule. In a human mass balance study, all human circulating and excreted metabolites were observed at <8% of total radioactivity. All metabolites have or are predicted to have ≤10 % of the potency of the parent molecule for JAK1/3 inhibition. In RA patients, the inter-subject variability in tofacitinib AUC(0-∞) is moderate (% coefficient of variation of 27%).

The clinical development program was designed to optimize a BID regimen of tofacitinib for the treatment of RA. The rationale for BID dosing is based on nonclinical and clinical biomarker (e.g. C-reactive protein) and outcome (e.g. disease activity score) data indicating the duration of pharmacodynamic (PD) activity of tofacitinib is longer than its PK half-life and that partial and intermittent inhibition of cytokine pathways over the dosing interval is sufficient to elicit sustained PD activity.

A summary of tofacitinib PK parameters (peak concentration (Cmax) and area under the concentration-time curve (AUC)) indicating the magnitude of change (and 90% confidence intervals) for various intrinsic and extrinsic factors relative to their corresponding reference values is presented in Figure 2. These data were derived from Phase 1 studies or population PK analysis of Phase 2 data in RA patients. The various intrinsic factors include age, weight, gender, race, and renal and hepatic impairment and extrinsic factors include food and drug interactions. A point estimate of 1 indicates no change in the PK parameter while a value greater than 1 indicates an increase and a value less than 1 indicates a decrease in the PK parameter. For example, coadministration of ketoconazole, a potent CYP3A4 inhibitor, with tofacitinib resulted in an approximate doubling of tofacitinib AUC relative to administration of tofacitinib alone; this is shown as a point estimate of approximately 2. Recommendations regarding dose adjustments or restrictions are made to achieve concentrations similar to those seen with the recommended 5 and 10 mg BID doses.

Figure 2. Tofacitinib Dosing Recommendations Based on Pharmacokinetic Data



Reference values for weight, age, gender, and race comparisons are 70 kg, 55 years, male and White, respectively; reference group for renal and hepatic impairment data are subjects with normal renal or hepatic function, respectively; reference group for DDI and food effect studies is administration of tofacitinib alone, Mod=moderate; Sev=severe; Imp=Impairment, Subjects with renal impairment were classified based on estimated creatinine clearance as mild (>50 and ≤80 mL/min), moderate (≥30 and ≤50 mL/min) and severe (<30 mL/min). Subjects with hepatic impairment were classified based on Child Pugh scores (A for mild, B for moderate).

7.1. Intrinsic Factors

- Based on the small magnitude of differences in AUC, tofacitinib does not require dose modification or restrictions for age, weight, gender, race, mild and moderate renal impairment or mild hepatic impairment in the adult RA population. Patients with CYP2C19 polymorphism also do not need dose adjustments due to small (<20%) differences in systemic exposure.

- It is recommended that tofacitinib dose should not exceed 5 mg BID for patients with severe renal impairment or moderate hepatic impairment due to the increased AUC relative to normal subjects. In clinical trials, tofacitinib was not studied in RA patients with baseline creatinine clearance (estimated by Cockcroft-Gault equation) less than 40 ml/min.

- Tofacitinib was not evaluated in subjects with severe hepatic impairment because of the risk of immunosuppressing patients who are already at risk of infection from their hepatic disease and the significant contribution of hepatic metabolism (approximately 70%) to the total clearance of tofacitinib. Therefore, tofacitinib is not recommended in patients with severe hepatic impairment.

7.2. Extrinsic Factors

7.2.1. Food

Tofacitinib can be administered with or without food. Coadministration of tofacitinib with a high fat meal resulted in no changes in AUC, while C_{max} was decreased by approximately 30%. The magnitude of decrease in C_{max} is not considered to be clinically relevant and no dosage adjustments or time restrictions between meal and drug intake are necessary. All pivotal efficacy and safety trials with tofacitinib have been performed without regard to meal.

7.2.2. Drug-Drug Interactions

Potential of Other Drugs to Influence the PK of tofacitinib

Since the metabolism of tofacitinib is primarily mediated by CYP3A4 (accounting for ~53% of total clearance) and by CYP2C19 (accounting for ~17% of total clearance), inhibitors or inducers of CYP3A4 are likely to alter the systemic exposure of tofacitinib.

- It is recommended that tofacitinib dose should not exceed 5 mg BID in patients receiving potent inhibitors of CYP3A4 (e.g., ketoconazole).

- Tofacitinib dose should not exceed 5 mg BID in patients receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 as well as potent inhibition of CYP2C19 (e.g., fluconazole).

- Coadministration of tofacitinib with potent inducers of CYP3A4 (e.g., rifampin) may result in loss of or reduced clinical response.

- No dosage adjustments are required for tofacitinib when coadministered with methotrexate.

- No dosage adjustments are needed when tofacitinib is coadministered with inhibitors of P-glycoprotein (P-gp).

Potential of tofacitinib to Influence the PK of Other Drugs

The potential for tofacitinib to affect the PK of other drugs, including those metabolized by CYP450 isoforms or eliminated renally, is low. The drugs evaluated for interactions in humans included methotrexate, midazolam, oral contraceptives and metformin.

- In vitro data indicate that tofacitinib does not inhibit or induce the CYP450 system. These results were confirmed by a human drug interaction study with midazolam, a highly sensitive CYP3A substrate.

- Human drug interaction studies have also shown that tofacitinib does not significantly affect the PK of MTX, oral contraceptives (ethinyl estradiol and levenorgestrel) or metformin.

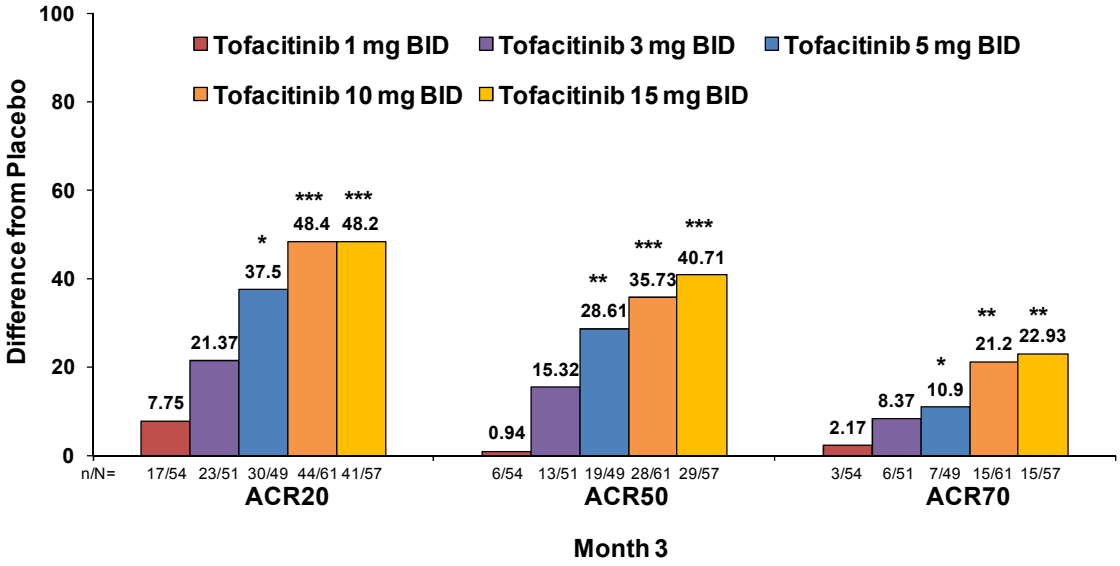
- In the RA population, the clearance of tofacitinib is time invariant, indicating that the cytokine mediated down-regulation of CYP450, seen in inflammatory diseases such as RA, is not normalized by tofacitinib. Therefore, tofacitinib is not expected to result in clinically relevant increases in the metabolism of CYP450 substrates in RA patients.

- At therapeutic concentrations, in vitro studies have shown that the potential for tofacitinib to inhibit transporters such as P-glycoprotein, organic anionic transporting polypeptides 1B1 or 1B3, or organic cationic transporter 2 is also low.

7.3. Dose Selection for Phase 3 Studies

The selection of 5 mg and 10 mg BID doses for the Phase 3 program was supported by a robust dose-finding program designed to evaluate the safety and efficacy of tofacitinib over a wide range of doses. Five placebo-controlled, randomized Phase 2 studies were performed, in which tofacitinib was given as monotherapy or in combination with background MTX. The Phase 2 program included approximately 1600 patients, and evaluated tofacitinib doses from 1 mg to 30 mg twice daily, for treatment durations ranging between 6 weeks and 6 months. The ACR responses from a representative monotherapy dose-finding study (Study 1035) are displayed in Figure 3. The study showed a clear dose response for all three ACR endpoints (ACR 20, ACR 50 and ACR 70), with doses ≥5 mg providing statistically significant efficacy versus placebo, while the 15 mg dose did not provide substantial improvements over the 10 mg dose. Model-based methods were also applied to characterize the dose response profile with improved precision to further inform the selection of 5 and 10 mg BID doses for Phase 3 studies (Tan, 2011).

Figure 3. ACR Responses from a Representative Dose Finding Study



*p≤0.05; **p<0.001; ***p<0.0001 vs placebo (unadjusted)

8. CLINICAL EFFICACY

The efficacy data demonstrate that:

- Relative to placebo, tofacitinib 5 mg or 10 mg BID treatment resulted in consistent, statistically significant and clinically meaningful improvements in multiple domains that are relevant to patients and practitioners:
    - Signs and symptoms, as measured by multiple endpoints, including ACR20 (primary), ACR50, and ACR70 response rates and the proportion of patients achieving DAS28-4(erythrocyte sedimentation rate[ESR]) <2.6 (primary).
    - Physical function status of patients as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI, primary).
    - Fatigue, as measured by the Functional Assessment of Chronic Illness Therapy – Fatigue scale (FACIT-fatigue). Significant improvement in fatigue relative to placebo was demonstrated for both tofacitinib 5 and 10 mg BID dose groups at Month 3 in each of the Phase 3 trials.
    - Health related quality of life, as measured by the short form SF-36 health survey. Statistically significant improvement at Month 3 was demonstrated for at least one tofacitinib dose group (5 or 10 mg BID) relative to the placebo group for all SF-36 domains and their components in each of the Phase 3 trials.
- Inhibition of the progression of structural damage as measured by changes from baseline in the van der Heijde modified Total Sharp score (mTSS) was a primary endpoint in a single Phase 3 study, 1044/Scan study. The difference from placebo in mean mTSS changes at Month 6 (primary) was statistically significant for the 10 mg BID group. The proportion of patients who did not have radiographic progression at Months 6 and 12 was significantly different from placebo for both the 5 and 10 mg BID groups (nominal p-values <0.05). Effect of tofacitinib on inhibition of the progression of structural damage was maintained for up to 12 months.
- Over a range of clinical efficacy measures, tofacitinib 5 and 10 mg BID provided similar or better efficacy than adalimumab 40 mg SC every other week.
- Tofacitinib is effective in patients with RA when used alone or in combination with traditional DMARDs.
- Tofacitinib is effective in patients with RA with a range of prior treatment experience including:
    - DMARD (including but not exclusively MTX-inadequate responders)
    - TNF inhibitor-inadequate responders

- Efficacy was consistent across subsets of gender, age (18-44, 45-64 and ≥65), race (white, black, Asian, and other), different weight or BMI groups, predefined regions (US, Europe/Canada, Latin America, rest of the world), and a range of baseline disease characteristics.

- Onset of effects (significantly different from placebo) was detected as early as:

  - 2 weeks in reducing signs and symptoms

  - 2 weeks in improving physical function

  - 1 month in improving fatigue measures

  - 3 months (the earliest time point of evaluation) in improving health related quality of life measures.

- Persistence of efficacy for tofacitinib 5 mg and 10 mg BID in reducing signs and symptoms and improving physical function was demonstrated

  - Up to 3 years in reducing signs and symptoms and improving physical function

  - Up to 12 months in improving fatigue and other health related quality of life measures.

- Across clinical efficacy measures, patients treated with 10 mg BID of tofacitinib consistently demonstrated improvement over 5 mg BID-treated patients. Greater benefits of treatment with 10 mg BID versus 5 mg BID were shown in the more stringent measures such as ACR70 and DAS28-4(ESR) <2.6 response rates.

These results are derived from a total of five Phase 3 and four Phase 2 multicenter, randomized, double-blind, placebo-controlled studies of tofacitinib, covering a range of treatment paradigms and previous treatment experience and conducted in approximately 4700 patients with rheumatoid arthritis (Table 6). Eight of the 9 studies evaluated tofacitinib in patients who had inadequate response to at least one nonbiologic or biologic DMARD, usually MTX; one study, the 1032/Step study, required patients to have been inadequate responders to at least one TNF inhibitor. Six of these 9 studies have a treatment design that includes administration of tofacitinib in combination with background DMARD therapy and in 3 other studies tofacitinib was administered as DMARD monotherapy. In addition, data are included from two ongoing, open-label, long-term extension studies, wherein 3227 patients continued to receive tofacitinib 5 mg or 10 mg BID.

Table 6. Overview of Clinical Studies Contributing to Efficacy Data

Study Number (Name)	Study Design/ Length	Treatment Groups	N
Phase 3			
Background DMARD Studies*			
A3921032 (Step)	MC, DB, PG, PC, R, Background MTX 6 Months	tofacitinib:	
		5 mg BID	133
		10 mg BID	134
		Placebo → tofacitinib 5 mg BID at 3 months	66
		Placebo → tofacitinib 10 mg BID at 3 months	66
A3921044‡ (Scan)	MC, DB, PG, PC, R, Background MTX 24 Months‡	tofacitinib:	
		5 mg BID	321
		10 mg BID	319
		Placebo → 5 mg	81
		Placebo →10 mg	79
		NR advance to next period at 3 months, All advance to next period at 6 months	
A3921046 (Sync)	MC, DB, PG, PC, R, Background DMARD 12 Months	tofacitinib:	
		5 mg BID	318
		10 mg BID	318
		Placebo → 5 mg	79
		Placebo → 10 mg	80
		NR advance to next period at 3 months, All advance to next period at 6 months	
A3921064 (Standard)	MC, DB, PG, PC, R, Background MTX 12 Months	tofacitinib:	
		5 mg BID	204
		10 mg BID	201
		Placebo → 5 mg	56
		Placebo → 10 mg	52
		Adalimumab 40 mg sc QOW	204
		NR advance to next period at 3 months, All advance to next period at 6 months..	
Monotherapy Studies			
A3921045 (Solo)	MC, DB, PG, PC, R 6 Months	tofacitinib	
		5 mg BID	244
		10 mg BID	245
		Placebo →5 mg tofacitinib at 3 months,	61
		Placebo → 10 mg BID tofacitinib at 3 months	61
Phase 2			
Background DMARD Studies*			
A3921025	MC, DB, PG, PC, R, Background MTX 6 Months	tofacitinib:	
		1 mg BID	71
		3 mg BID	68
		5 mg BID	71
		10 mg BID	75
		15 mg BID	75
		20 mg QD	80
		Placebo	69
		NR on Placebo, tofacitinib 1 and 3 mg BID and 20 mg QD → 5 mg BID at 3 months.	

Table 6. Overview of Clinical Studies Contributing to Efficacy Data

Study Number (Name)	Study Design/ Length	Treatment Groups	N
A3921039	MC (in Japan), DB, PG, PC, R, Background MTX 3 Months	tofacitinib :	
		1 mg BID	28
		3 mg BID	28
		5 mg BID	28
		10 mg BID	28
		Placebo	28
Monotherapy Studies			
A3921035	MC, DB, PG, PC, R 6 Months	tofacitinib:	
		1 mg BID	54
		3 mg BID	52
		5 mg BID	50
		10 mg BID	61
		15 mg BID	57
		Adalimumab 40 mg sc QOW for 10 weeks →5 mg BID at 3 months	53
		Placebo	59
		NR on Placebo, tofacitinib 1 and 3 mg BID →5 mg BID at 3 months.	
A3921040	MC (in Japan), DB, PG, PC, R 3 Months	tofacitinib:	
		1 mg BID	53
		3 mg BID	53
		5 mg BID	52
		10 mg BID	53
		15 mg BID	54
		Placebo	53
Long-Term Extension Studies			
A3921024 (Sequel)	LT, OL	tofacitinib 5 mg BID tofacitinib 10 mg BID	2823[†]
A3921041	LT, OL (in Japan)	tofacitinib 5 mg BID tofacitinib 10 mg BID	404[†]

N = number of patients randomized, MC = multicenter, DB = double blind, PG = parallel group, PC = placebo controlled, R = randomized, NR = nonresponder (patient who failed to improve at Month 3 by at least 20% from baseline in the number of swollen and tender/painful joint count), MTX = methotrexate, DMARD = disease modifying antirheumatic drug, sc = subcutaneous, QOW = every other week, LT = long term, OL = open label

***** In addition to their randomized treatment, all patients in background DMARD studies also received methotrexate

[†]Number of patients for 5 mg and 10 mg BID combined

[‡]The study is ongoing. 1-year analysis is provided.

8.1. Characteristics of the Study Population

The RA development program was global in scope, with patients participating from US, Europe, Latin America, and the rest of the world (mostly Asia). Patients treated with tofacitinib 5 mg BID, 10 mg BID, or placebo in the Phase 2/3 trials were predominantly from US (20%), Europe/Canada (34%), and Latin America (15%). The consistency of the clinical presentation of RA and the widespread use of the ACR classification criteria for diagnosis of RA across these geographic regions and the standardization of care required by the individual protocols insure that the evidence of efficacy observed in the overall program is broadly applicable.

The efficacy studies enrolled DMARD-experienced patients who had moderately to severely active RA, satisfying the ACR classification criteria and with at least a minimum number of swollen and tender joints and an increased acute phase reactant, i.e. ESR and/or CRP. Rates of rheumatoid factor and anti-CCP positivity are consistent with those reported. Monotherapy studies required discontinuation of all background DMARDs (studies A3921035 and 1045/Solo exempted stably dosed background antimalarials). Background MTX studies required discontinuation of all DMARDs other than MTX. RA patients were allowed to receive stably-dosed NSAIDs and "low dose" oral glucocorticoids, i.e. ≤10 mg/day prednisone equivalent, consistent with rheumatology practice worldwide. All studies required discontinuation of potent immunosuppressants, such as azathioprine and calcineurin inhibitors.

The program included patients aged 18 to 86 years, the majority of whom had long standing RA disease (mean of 7 to 13 years in the Phase 3 study treatment groups) and high disease activity. Approximately 15% of the participants were ≥65 years old at study entry, a group known to be at higher risk of certain adverse events. The mid-range mean degree of disability, as assessed by Health Assessment Questionnaire Disability Index (HAQ-DI), is consistent with expectations for an inadequately treated RA population with nearly a decade of disease prior to study entry.

Exclusion criteria were similar across the Phase 2 and Phase 3 studies and are consistent with the intended patient population to be treated after registration. Restrictions for many common medical co-morbidities, e.g. diabetes mellitus, hypertension, hypercholesterolemia, ischemic heart disease, congestive heart failure, obstructive or restrictive lung disease, were minimized in order to include patients similar to those likely to use tofacitinib after registration. Severely functionally impaired patients (Steinbrocker class IV) were excluded. Serious or severe hepatic and renal disease were excluded, but these are not common in the RA clinic population. Restrictions to treatments for comorbid conditions were largely mandated to avoid anticipated pharmacokinetic drug interactions. Pre-existing immunodeficiency disorders, active and recurrent infections (with particular attention to TB), and malignancies were exclusion criteria. Specific targeted screening was undertaken for TB; malignancy was identified by medical history and physical examination.

In the Phase 3 program, approximately 8% of patients had diabetes, 24% had hyperlipidemia, and 23% had hypertension (per JNC7 classification) at baseline. Approximately 24% of patients had a Framingham 10-year coronary heart disease risk > 5%; 10-13% had a risk >10% at baseline. The CV risk profile at baseline was comparable across all Phase 3 treatment groups.

In summary, the study population in the tofacitinib RA program was closely representative of the worldwide inadequately treated RA population, and patients were managed within the program in a manner consistent with conventional rheumatology practice. Patients suffered from a common spectrum of co-morbid conditions, and received treatment for these co-morbid conditions, with relatively few restrictions. Therefore the data derived from this RA program should be predictive of the results that are expected post-registration.

8.2. Study Design

8.2.1. Background DMARD Studies

Phase 3 Background DMARD Studies

The primary endpoints for the Phase 3 background DMARD studies were signs and symptoms as assessed by ACR20 response rates at Month 3 or 6, physical function as assessed by HAQ-DI at Month 3, and rates of DAS28-4(ESR) <2.6 as measured at Month 3 or 6. The 1044/Scan study also assessed progression of structural damage using modified Sharp scoring of hand and feet radiographs with the primary time point at Month 6. Further details of these endpoints are provided in Section 8.3 below. Patient numbers cited below refer to number of patients who were treated with study drug during the studies.

Scan Study (A3921044): An ongoing 2-year study in 797 patients with moderate to severe active RA who had an inadequate response to MTX. These patients received tofacitinib 5 or 10 mg BID or placebo added to background MTX treatment. Data from the planned 1-year analysis is included in the original submission. At the Month 3 visit, non-responding placebo patients were advanced in a blinded fashion to a second predetermined treatment of tofacitinib 5 or 10 mg BID. At the end of Month 6, all placebo patients were advanced to their second predetermined treatment in a blinded fashion. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, change from baseline in mean modified Total Sharp Scores at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

Sync Study (A3921046): A 12-month study in 792 patients with moderate to severe active RA who had an inadequate response to a nonbiologic DMARD. These patients received tofacitinib 5 or 10 mg BID or placebo added to background DMARDs (excluding potent immunosuppressive treatments such as azathioprine or cyclosporine). Placebo patients were advanced as in the Scan study. The co-primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, changes in HAQ-DI at Month 3 and rates of DAS28-4(ESR) less than 2.6 at Month 6 compared to placebo controls.

Standard Study (A3921064): A 12-month study in 717 patients with moderate to severe active RA who had an inadequate response to MTX. These patients received tofacitinib 5 or 10 mg BID, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX. Placebo patients were advanced as in the Scan study. The co-primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6 compared to placebo controls.

Step Study (A3921032): A 6-month study in 399 patients with moderate to severe active RA who had an inadequate response to at least one approved TNF-inhibitor biologic agent. These patients received tofacitinib 5 or 10 mg BID or placebo added to background MTX treatment. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of tofacitinib 5 or 10 mg BID. The

primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, HAQ-DI, and DAS28-4(ESR) less than 2.6 compared to placebo controls.

Phase 2 Background DMARD Studies

Study A3921025: A 6-month dose-finding study in 507 patients with moderate to severe active RA who had an inadequate response to MTX. These patients received one of the following doses of tofacitinib (1, 3, 5, 10, or 15 mg BID or 20 mg QD) or placebo added to background MTX treatment. Non-responders to tofacitinib dosed 1 or 3 mg BID or 20 mg QD or to placebo were all advanced to tofacitinib 5 mg BID at 12 weeks. The primary endpoint was ACR20 response at Month 3.

Study A3921039: A 3-month dose-finding study conducted in Japan in 136 patients with moderate to severe active RA who had an inadequate response to MTX treatment. These patients received one of the following doses of tofacitinib (1, 3, 5, or 10 mg BID) or placebo. ACR20 response was measured at Month 3. The primary endpoint was ACR20 response at Month 3.

8.2.2. Monotherapy Studies

In the monotherapy studies, all patients were required to have failed at least 1 DMARD (nonbiologic or biologic) treatment. All monotherapy studies evaluated the primary endpoint of ACR20 at Month 3. The Phase 3 monotherapy 1045/Solo study had additional primary efficacy endpoints of HAQ-DI and DAS28-4(ESR) <2.6 at Month 3.

Phase 3 Monotherapy Study

Solo Study (A3921045): A 6-month monotherapy study in 610 patients with moderate to severe active RA who had an inadequate response to a DMARD (nonbiologic or biologic). These patients received tofacitinib 5 or 10 mg BID or placebo. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of tofacitinib 5 or 10 mg BID. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, changes in HAQ- DI, and rates of DAS28-4(ESR) <2.6.

Phase 2 Monotherapy Studies

Study A3921035: A 6-month monotherapy study in 384 patients with moderate to severe active RA who had an inadequate response to a DMARD (nonbiologic or biologic). Patients received one of the following doses of tofacitinib (1, 3, 5, 10, or 15 mg BID) or adalimumab 40 mg SC injection (monotherapy) every other week or placebo. Patients on adalimumab, and non-responders to tofacitinib dosed 1 or 3 mg BID or to placebo were all advanced to tofacitinib 5 mg BID at Week 12. The primary endpoint was ACR20 response at Month 3.

Study A3921040: A 3-month monotherapy study conducted in Japan in 317 patients with moderate to severe RA who had an inadequate response to at least 1 DMARD (nonbiologic or biologic, including MTX). Patients received one of the following doses of tofacitinib (1, 3, 5, 10, or 15 mg BID) or placebo. The primary endpoint was ACR20 response at Month 3.

8.2.3. Long-Term Extension Studies

Patients participating in Phase 2 and 3 studies have the option to join the long-term, open-label studies to continue treatment with tofacitinib.

Study A3921024: An ongoing long-term, open-label study in up to 4000 patients to further assess the long-term safety and efficacy of tofacitinib in patients with moderate to severe RA who have completed participation in a randomized study of tofacitinib for the treatment of RA. Patients from Phase 2 studies receive tofacitinib 5 mg BID, and patients from Phase 3 studies receive tofacitinib 10 mg BID (with the exception of China, where patients are dosed at 5 mg BID). Tofacitinib doses could be adjusted for safety concerns, lack of tolerance or lack of efficacy. As of 29 September 2011, there were 3088 patients participating.

Study A3921041: An ongoing long-term, open label study conducted in Japan in up to 500 patients to further assess the long-term safety and efficacy of tofacitinib in patients with moderate to severe RA who have completed the Japan Phase 2 studies A3921039 and A3921040 and the global Phase 3 1044/Scan study. Patients continue to receive tofacitinib 5 mg BID. Tofacitinib doses could be adjusted for safety concerns, lack of tolerance or lack of efficacy. As of 29 September 2011, there were 427 patients participating.

Tofacitinib 5 mg and 10 mg were administered orally twice daily in these RA studies; 5 mg BID and 5 mg, as well as 10 mg BID and 10 mg, may be used interchangeably for treatment designation in the rest of the document.

8.3. Efficacy Evaluations

Primary endpoints in the Phase 3 studies are summarized below.

Table 7. Primary Efficacy Endpoints and their Time Points for Phase 3 Studies

Study	Proportion of Patients Achieving ACR20 Response	Change from Baseline in Total Sharp Score	Change from Baseline in HAQ-DI	Proportion of Patients Achieving DAS28-4(ESR) < 2.6
1032/Step	Month 3	n/a	Month 3	Month 3
1044/Scan	Month 6	Month 6	Month 3	Month 6
1045/Solo	Month 3	n/a	Month 3	Month 3
1046/Sync	Month 6	n/a	Month 3	Month 6
1064/Standard	Month 6	n/a	Month 3	Month 6

The primary time point for HAQ-DI was at Month 3 for all Phase 3 studies, while for all other primary endpoints, Month 3 was the primary time point for studies with 6-months duration and Month 6 for studies with at least 12-months duration.

Tofacitinib efficacy was evaluated using validated measures as recommended in the FDA (February 1999) and EMA (December 2003) guidances for industry on clinical development programs for products for the treatment of RA.

8.3.1. RA Signs and Symptoms Assessments

8.3.2. ACR20, ACR50, ACR70

The American College of Rheumatology's ACR20 criteria for assessing response to treatment and improvement in RA are defined as at least a 20% improvement in tender and swollen joint counts and at least a 20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant. Similarly, ACR50 and 70 are calculated with the respective percent improvement. The acute-phase reactant used in this program for calculation of ACR responses was the CRP.

The specific components of the ACR assessments that were used in the tofacitinib studies are:

- Tender/painful joint count
- Swollen joint count
- Patient's assessment of arthritis pain
- Patient's global assessment of arthritis
- Physician's global assessment of arthritis
- C-Reactive Protein (CRP)
- Health Assessment Questionnaire-Disability Index (HAQ-DI)

Disease Activity Score (DAS)

DAS28 assessments are composite measures of disease activity that have utility in the emerging practice of using structured patient management paradigms, which employ achievement of specific disease activity targets. Both DAS28-4(ESR) and DAS28-3(CRP) are commonly used, with frequently utilized disease activity score targets of <2.6 and ≤ 3.2. Components of DAS28-4(ESR) include tender/painful joint (28), swollen joint count (28), ESR as the acute phase reactant, and the Patient Global Assessment of Arthritis. Components of DAS28-3(CRP) include tender/painful joint (28), swollen joint count (28), and CRP as the acute phase reactant. Per agreement with the FDA, DAS28-4(ESR) <2.6 was used as one of the primary endpoints in the Phase 3 studies.

8.3.3. Radiographic Assessment of Joint Damage

Radiographs of hands and feet were performed at Baseline and at specified time points during the 1044/Scan study. Radiographs were scored using the van der Heijde modified Sharp method by two independent central assessors who were blinded to patient treatment assignment and acquisition sequence. The scores recorded by these two readers were

averaged and compared by time point to determine radiographic progression. The Scan study is ongoing and only data through Month 12 were analyzed and reported here.

8.3.4. Physical Function Assessment

Health Assessment Questionnaire – Disability Index (HAQ-DI): The HAQ-DI assesses the degree of difficulty a patient has experienced during the previous week in 8 domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities.

8.3.5. Patient Reported Outcomes

Additional measures of patient reported outcomes include the SF-36 Health Survey, Medical Outcomes Study (MOS) Sleep Scale, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, EuroQol EQ-5D Health State Profile, RA Healthcare Resource Utilization Questionnaire (RA-HCRU), and the Work Limitations Questionnaire (WLQ).

8.4. Durability of Efficacy Response

Durability of efficacy was assessed using ACR20, ACR50, ACR70 and DAS28-based response rates in studies >6 months in duration (Studies 1044/Scan, 1046/Sync, 1064/Standard) as the proportion of patients who first achieved the response at each post baseline visit (e.g., at Month 1) and, of these, the proportion of patients who sustained the level of response for the subsequent consecutive visits (e.g., Month 3 to Month 12, and Month 3 to Month 24).

Durability of response was also assessed in the LTE studies A3921024 and A3921041 using ACR20, ACR50, and ACR70 response rates (with Baseline defined as Baseline in the patient's qualifying randomized Pfizer Phase 2/3 study), mean HAQ-DI, and mean DAS28-4(ESR) at Month 1, 2, 3, and every 3 months thereafter.

8.5. Statistical Analyses

In each of the pivotal Phase 3 studies, patients were randomized to one of four sequences (and a fifth additional sequence in the 1064/Standard study) as shown in Table 8.

Table 8. Randomization Sequences in the Phase 3 Studies

Sequence	Treatment	
	Period 1	Period 2
1	Tofacitinib 5 mg BID	Tofacitinib 5 mg BID
2	Tofacitinib 10 mg BID	Tofacitinib 10 mg BID
3	Placebo BID	Tofacitinib 5 mg BID
4	Placebo BID	Tofacitinib 10 mg BID
5 (Standard study only)	Adalimumab 40 mg, QOW SC injection	Adalimumab 40 mg, QOW SC injection

BID=twice daily; QOW = every other week, SC = subcutaneous

In each study, a patient advanced from one dosing period to another. This was mandatory at Month 3 for studies 1032/Step and 1045/Solo. It occurred as early as Month 3 and was mandatory at Month 6 for studies 1044/Scan, 1046/Sync and 1064/Standard.

In Studies Scan, Sync and Standard, advancement occurred at Month 3 if a patient was a nonresponder. A "nonresponder" is specifically defined as a patient who failed to improve at Month 3 by at least 20% from baseline in the number of swollen and tender / painful joints.

While all nonresponders were advanced to study Period 2 at Month 3, only placebo patients changed study medication, advancing from placebo to tofacitinib 5 mg BID or to tofacitinib 10 mg BID.

Regardless of study and, regardless of whether mandatory or not, advancement was always executed in a blinded fashion according to the sequence the patient was randomized to at baseline.

Primary analyses were performed by combining placebo sequence cohorts for periods that included a placebo treatment period into a single placebo group, and this combined group was then compared to the 10 mg BID or 5 mg BID groups. Statistical analyses in the Phase 2 RA studies were generally similar to those in Phase 3 studies.

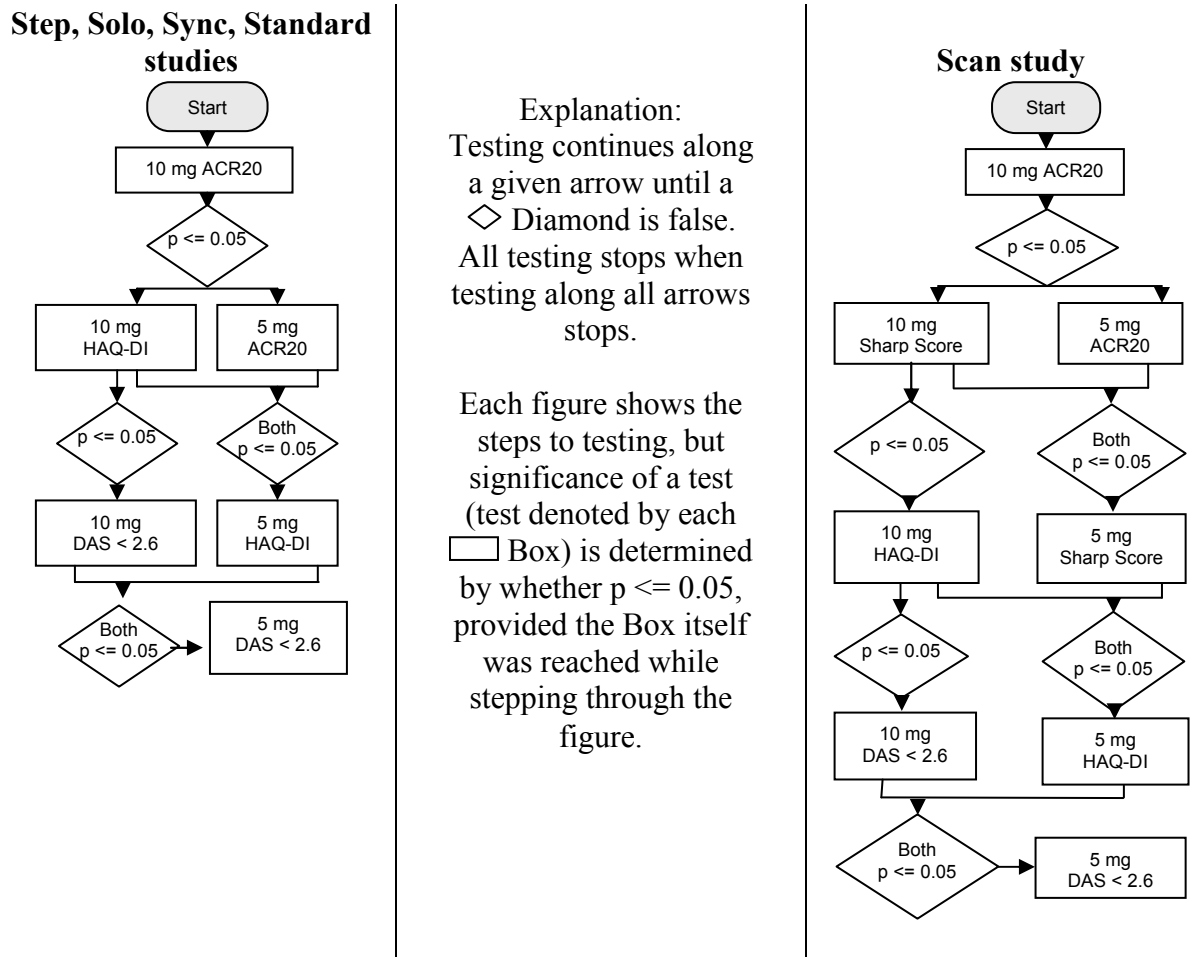
The sequence of analysis of the primary endpoints in all Phase 3 studies except 1044/Scan was 1) signs and symptoms as measured by the proportion of patients achieving an ACR20 response, 2) physical function as measured by the HAQ-DI, and 3) the proportion of patients achieving DAS28-4(ESR) <2.6. Secondary endpoints included ACR50 and 70 response rates, the proportion of patients achieving DAS28-4(ESR) ≤ 3.2, and mean change in DAS28-4(ESR) from baseline.

One-year data from the ongoing Scan study provides evidence of tofacitinib efficacy in inhibiting progression of structural damage by means of radiographs scored using the van der Heijde modified Sharp scoring system. The sequence of analysis of the primary endpoints in the Scan study was 1) signs and symptoms as measured by the proportion of patients achieving an ACR20 response, 2) inhibition of the progression of structural damage as measured by the mean change from baseline in modified Total Sharp Score (mTSS) at Month 6; 3) physical function as measured by the HAQ-DI, and 4) the proportion of patients achieving DAS28-4(ESR) <2.6. As will be discussed later in Section 8.10.1, in the 1044/Scan study, as a consequence of the step-down procedure, mean change from baseline in HAQ-DI and DAS28-4(ESR) <2.6 response rates were reported as statistically significant only for tofacitinib 10 mg BID group because mean change from baseline in mTSS, a primary endpoint, was statistically significant compared with placebo with the 10 mg BID dose, but not the 5 mg BID dose. However, the differences from placebo for the 5 mg group had nominally significant p-values for both these endpoints in that study.

The primary analysis step down procedure of Phase 3 studies, which determined statistical significance for the primary endpoints protecting the rate of type I error, is shown in Figure 4. Statistical significance can be claimed for a given endpoint only if the prior

endpoint in the sequence met the requirement for significance. Secondary analyses have not been subjected to the step-down procedure; their significance was declared nominally (no protection of Type I error) when p ≤0.05; such p-values are noted here as nominal p-values.

Figure 4. Primary Analysis Step Down Procedure



A3921032 = Step, A3921044 = Scan, A3921045 = Solo, A3921046 = Sync, A3921064 = Standard

8.5.1. Handling of Missing Data

The following methods of imputation were applied to all treatment sequences and not just to the placebo sequences.

As suggested by the FDA, a non-responder imputation [NRI] was applied to binary data. NRI was used to handle missing values for the calculation of the proportion of patients achieving ACR20, ACR50 and ACR70, and DAS28-4(ESR) < 2.6,. NRI sets response to "failure" when a patient withdraws for any reason; in studies >6-month duration where a patient could have advanced to tofacitinib at Month 3, NRI treats that advancement as if the patient had left the study at Month 3, setting response to "failure" as well. In the analysis, this was applied to all sequences, not just placebo sequences.

For calculation of the mean change from baseline in HAQ-DI, the longitudinal mixed effect linear model *implicitly* imputes for missing data under the assumption of "missing at random". There was no *explicit* imputation. For studies of 6 months duration where at Month 3 the patients all advanced to tofacitinib, the longitudinal model only included up to Month 3. For studies of >6 months duration, patients that advanced were treated as if they left the study and their post Month 3 data were set to missing. The model itself included up to Month 6, the last month where placebo responses were measured before all patients advanced to tofacitinib.

For calculation of mean change from baseline in mTSS, patients who discontinued from the 1044/Scan study prior to Month 6 or who were determined to be non-responders at Month 3, had their Month 6 measurements imputed using a linear extrapolation applied to the Baseline and last available post-baseline scores of their radiographs. In the case of non-responders, that was obtained at the time of advancement (Month 3). Linear extrapolation is a common method of imputation applied in analysis of Sharp Scores. Note that a similar approach was applied for Month 12, and that all values for placebo at Month 12 are extrapolated from Month 3 or Month 6.

8.6. Subject Disposition

The completion rates were generally similar across the treatment groups in each study and ranged from 72.7% to 89.9% among the treatment groups in the background DMARD studies. In the monotherapy studies, the completion rates were generally higher in the tofacitinib treatment groups (86.0% to 96.2%) than in the placebo groups (72.9% to 90.6%).

8.7. Baseline Disease Characteristics and Demographics

Baseline RA disease characteristics were balanced among treatment groups (tofacitinib 5 mg, tofacitinib 10 mg, placebo →5 mg, placebo →10 mg, and adalimumab (1064 only)) in each study. Ranges of mean baseline disearse characteristics among the treatment groups in each study are presented in Table 9.

Table 9. Baseline Disease Characteristics

Study	Range of Means across Treatment Groups						
	Mean Disease Duration (yrs)	Rheumatoid Factor + (%)*	Mean Tender Joint Count	Mean Swollen Joint Count	Mean HAQ-DI	Mean DAS28-4 (ESR)	Corticosteroid Use (%)
Background DMARD Studies							
Phase 3							
1044/Scan	8.8-9.5	75.2-79.7	22.6-24.1	14.0-14.5	1.23-1.41	6.25-6.34	51.9-63.9
1046/Sync	8.1-10.2	72.6-73.9	21.9-27.2	13.9-14.6	1.24-1.45	6.14-6.44	48.8-58.2
1064/Standard	6.9-9.0	66.8-67.4	26.1-28.5	16.4-16.9	1.36-1.53	6.33-6.56	59.8-71.4
1032/Step	11.2-13.0	60.6-65.7	26.7-29.7	15.1-19.3	1.50-1.66	6.29-6.59	54.5-65.4
Phase 2							
A3921025	7.5-11.8	64.6-79.3	21.5-24.8	14.1-16.5	1.2-1.6	5.98-6.37	45-64
A3921039	5.7-8.7	85.2-92.3	15.4-17.8	13.2-15.6	1.14-1.29	5.86-6.11	50.0-71.4
Monotherapy Studies							
Phase 3							
1045/Solo	7.3-8.6	52.5-71.3	28.4-29.4	16.3-17.7	1.48-1.58	6.63-6.71	55.7-65.6
Phase 2							
1035	7.7-10.8	62.7-75.4	24.1-27.1	14.9-17.4	1.4-1.6	6.3-6.6	51.0 -61.1
1040	6.4-11.0	82.7-86.5	13.6-18.6	11.3-15.3	1.19-1.50	5.83-6.41	56.6-79.2

Treatment groups include tofacitinib 5 mg, 10 mg, placebo →5 mg, placebo →10 mg, and adalimumab sequence groups in the studies.
*reported for tofacitinib 5 mg and 10 mg BID and placebo patients.

The mean disease duration of RA was somewhat longer in the 1032/Step study than in the 4 Phase 3 studies requiring an inadequate response to a DMARD; this result was not unexpected as this was the only study to require prior inadequate response to a TNF inhibitor as part of the inclusion criteria. The baseline disease characteristics of patients in the Phase 2 background DMARD studies and the Phases 2 and 3 monotherapy studies were similar to those in the Phase 3 background DMARD studies.

Baseline demographics were generally similar among the treatment groups in each study and similar between the studies (Table 10). The majority of the patients (55% to 86%) in each study were white. Exceptions to this were the two Phase 2 studies conducted only in Japan (background DMARD Study A3921039 and monotherapy Study A3921040), and worldwide 1044/Scan study, which included multiple Asian countries. Investigator sites for the 1032/Step and 1064/Standard studies were mainly located in the US and EU, accounting for the higher proportion of white patients in these studies.

Table 10. Demographic Characteristics

Study	N	Female (%)	Age (yrs) Mean (Range)	Race W/B/A/O (No. Subjects)	Weight (kg) Mean (Range)
Background DMARD Studies					
1044/Scan (1-Year Analysis)	800	84.9	[52.0-53.7]*(18-82)	368/24/338/67	65.6-70.3*
1046/Sync	792	81.4	52.3 (18-86)	439/15/275/63	70.5 (34.7-186.9)
1064/Standard	717	81.7	52.9 (18-83)	517/13/108/79	72.0 (34.5-162.0)
1032/Step	399	84.0	55.0 (20-84)	332/27/27/13	79.1 (43.0-188.0)
1025	507	80.1	[50.8-56.0]*(18-81)	438/11/0/58	69.6-76.2*
1039	136	86.0	[50.0-53.3]*(24-70)	0/0/136/0	52.6-55.8*
Monotherapy Studies					
1045/Solo	610	86.6	51.8 (21-81)	409/28/88/85	72.1 (30.5-157.0)
1035	384	86.7	[52.4-55.1]* (18-83)	294/9/35/46	65.7-75.7*
1040	317	83.3	53.4 (20-70)	0/0/317/0	54.4 (31.4-85.6)

Include all treatment groups in the studies.
*Range of mean across treatment groups

8.8. Prior Treatment for Rheumatoid Arthritis

All patients had to have received prior treatment with at least one DMARD (nonbiologic or biologic) to which they had an inadequate response. With the exception of Study Sync, all background DMARD studies required prior treatment with MTX. In Study 1046/Sync, patients were required to have prior treatment with a DMARD, and the majority had received MTX (84.3%). Other than the 1032/Step study, in which patients were required to have had an inadequate response to a TNF inhibitor, prior TNF inhibitor usage ranged from 6.6% to 15.9% across the Phase 3 background DMARD studies. Other prior biologic DMARD usage ranged from 2.1% to 11.5% in the Phase 3 background DMARD studies. When previous TNF inhibitor treatment was limited to a single TNF inhibitor, 29% to 49% of patients in the background DMARD studies discontinued the TNF inhibitor due to lack of efficacy.

In the monotherapy studies, all patients also had inadequate response to at least one DMARD (nonbiologic or biologic) treatment.

8.9. Concomitant RA Treatments

In all studies, patients were allowed to continue stable dosing of NSAIDs and low dose corticosteroids and analgesics. In the background MTX studies, 94%-99% received a single background DMARD (MTX). In the 1046/Sync study, in which MTX was not the required background treatment, 68% of patients received a single background DMARD, with MTX being the most frequent (51%) followed by leflunomide (10%). Also in this study, 27% of patients received 2 concomitant background DMARDs. The concomitant use of three or more DMARDs was low (0.0 – 4.7%).

8.10. Efficacy Results

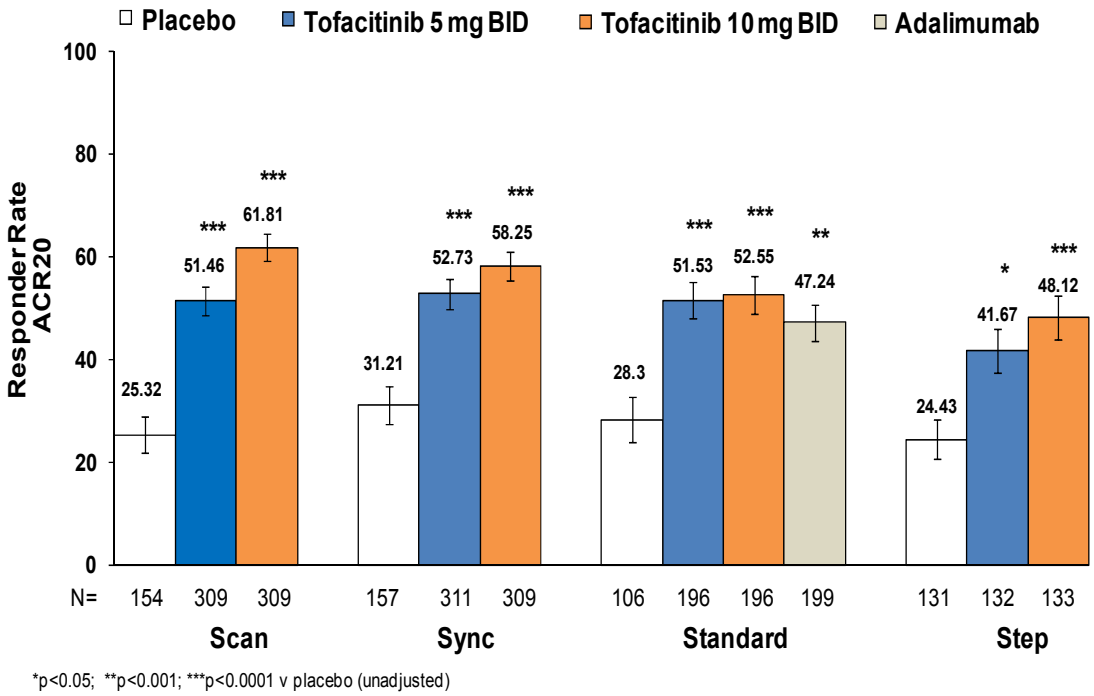
This section summarizes the overall efficacy results of Phase 3 studies. The Phase 2 studies were dose response studies and the results were generally similar and consistent with the Phase 3 results.

8.10.1. Efficacy Results for Background DMARD Studies

8.10.1.1. Signs and Symptoms: ACR Response

Both 5 and 10 mg tofacitinib dose groups demonstrated statistically significant and clinically meaningful reductions in signs and symptoms of RA over placebo in each of the Phase 3 studies and ACR20 response rates in the tofacitinib 10 mg BID groups were numerically greater than in the tofacitinib 5 mg BID groups. The primary endpoint of the proportion of patients achieving an ACR20 response at the primary time points, in the Phase 3 background DMARD studies, was statistically significantly different for both the tofacitinib 5 mg and 10 mg BID groups compared with the placebo group in each of the Phase 3 background DMARD studies (p-values ≤0.0025) (Figure 5). Response rates for the secondary endpoints of ACR50 (Figure 6) and ACR70 (Figure 7) were consistent with the ACR20 results in these background DMARD studies and were significantly greater in the tofacitinib treatment groups compared with the placebo group for all post baseline evaluation time points (nominal $p<0.05$). Overall, ACR50 and ACR70 response rates were consistently numerically higher in the 10 mg tofacitinib group compared with the 5 mg group for these studies.

Figure 5. ACR20 Response Rates at Primary Time Point – Phase 3 Background DMARD Studies



*p<0.05; **p<0.001; ***p<0.0001 v placebo (unadjusted)

A3921032 = Step, A3921044 = Scan, A3921046 = Sync, A3921064 = Standard
Primary time point is Month 6 for Scan, Sync and Standard studies and Month 3 for the Step study

Figure 6. ACR50 Response Rates at Primary Time Point – Phase 3 Background DMARD Studies

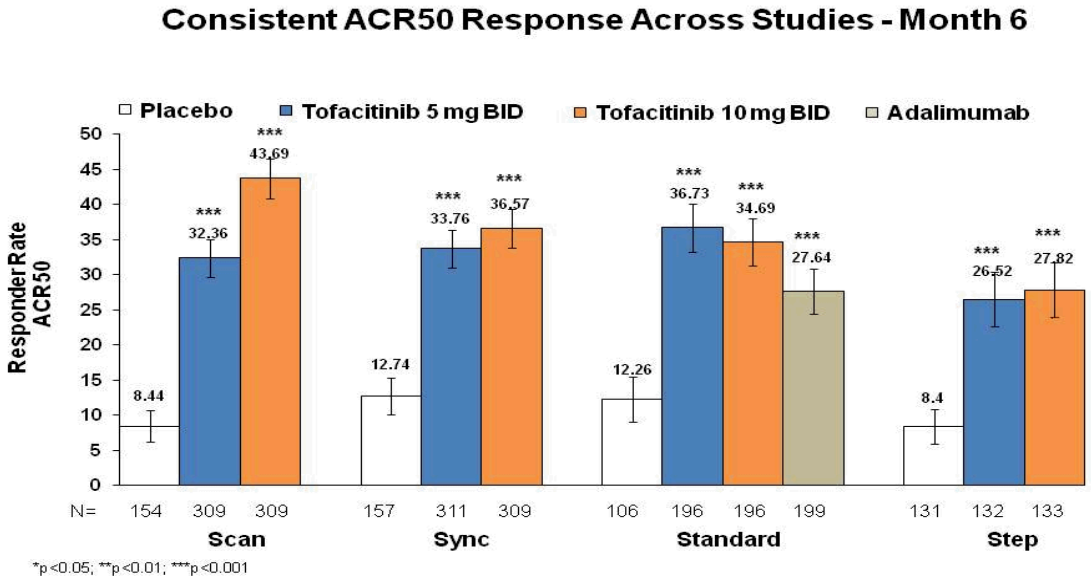
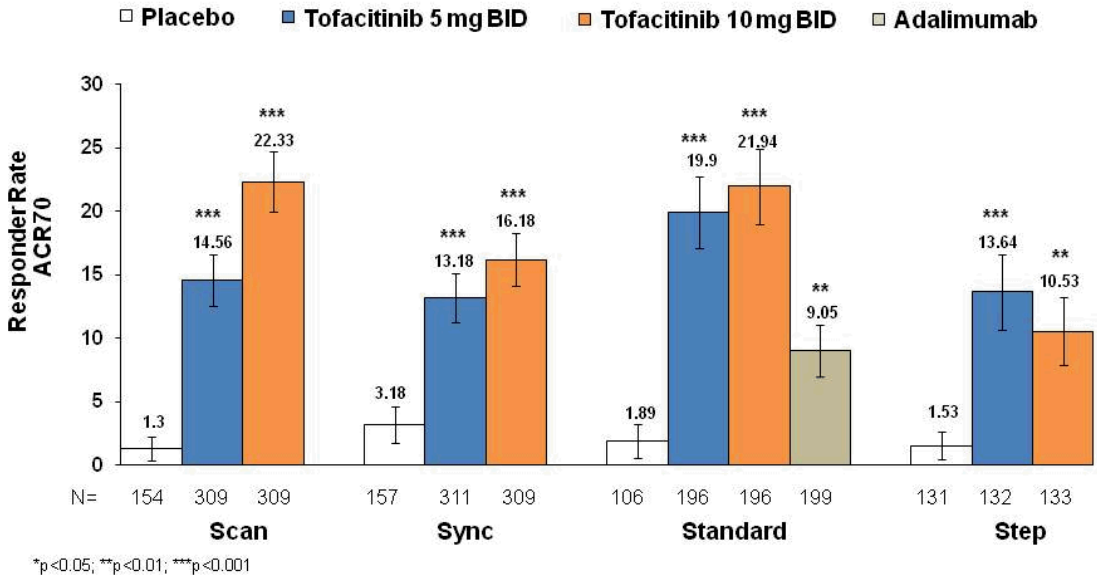


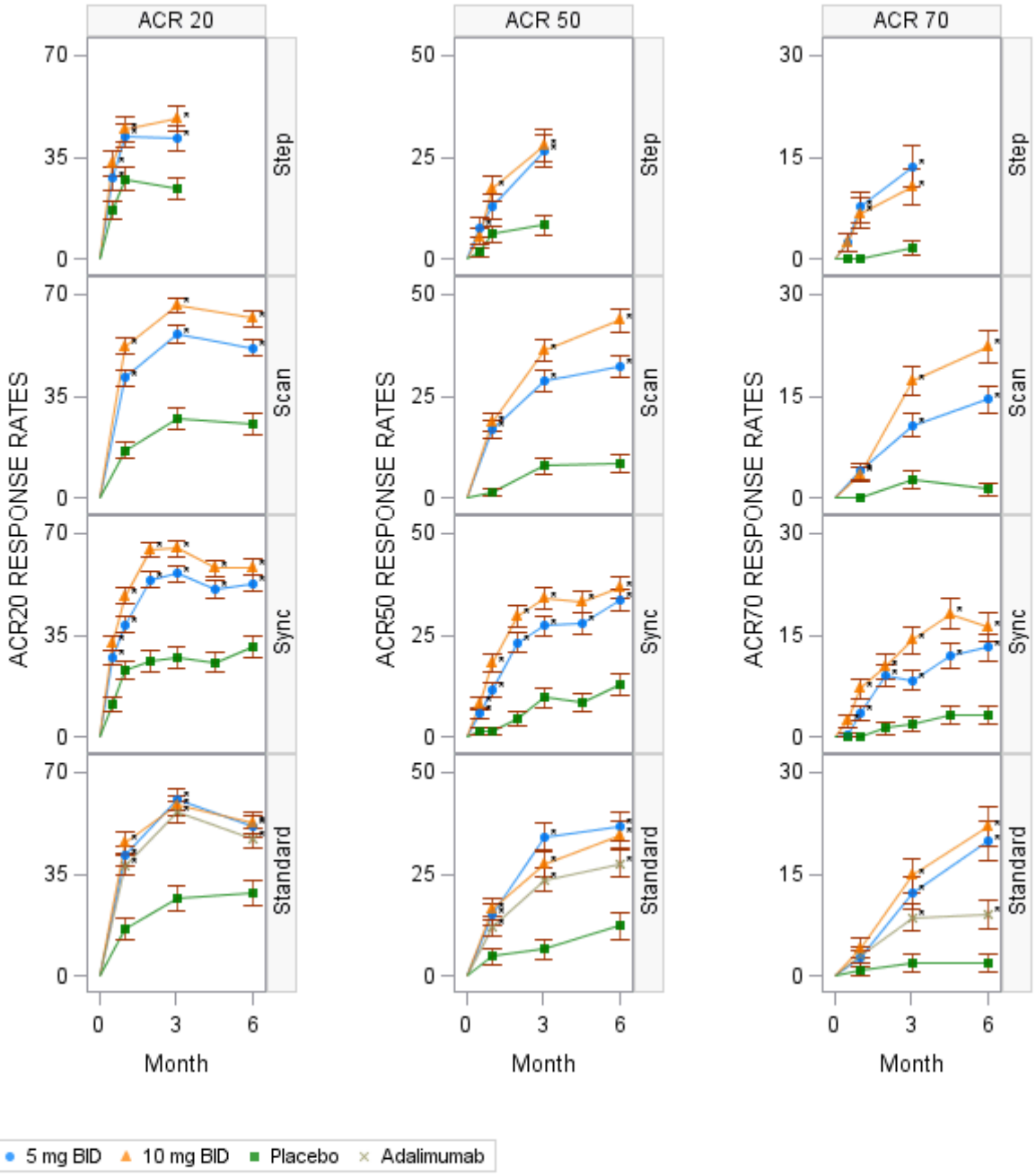
Figure 7. ACR70 Response Rates at Primary Time Point – Phase 3 Background DMARD Studies



A3921032 = Step, A3921044 = Scan, A3921046 = Sync, A3921064 = Standard
Primary time point is Month 6 for Scan, Sync and Standard studies and Month 3 for the Step study

Statistically significant differences from placebo in ACR20 response rates for both the 5 mg and 10 mg tofacitinib groups were seen as early as Week 2 or Month 1 (the first assessment time points) in the studies and maintained through the double blind treatment period (nominal p-values <0.05). Similar results were observed for ACR50 response rates. ACR20, ACR50, and ACR70 response rates at each assessment time points up to the primary time points in the background DMARD studies are shown in Figure 8.

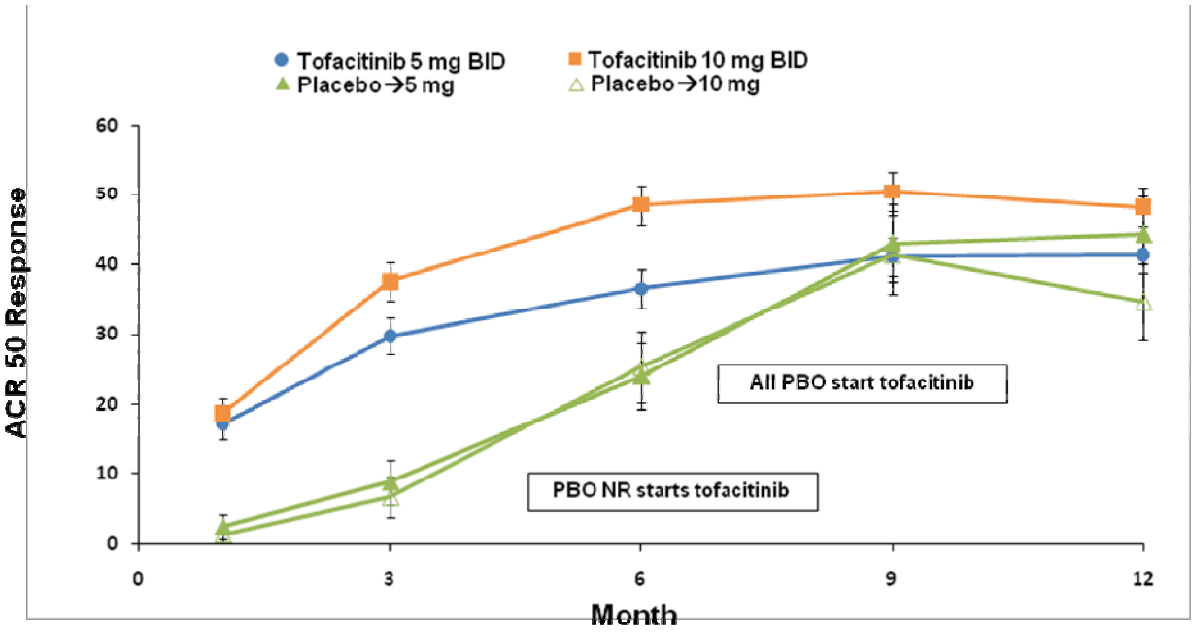
Figure 8. ACR Response Rates (%) (±SE) (Comparisons to Placebo) – Background DMARD Studies



* $p \leq 0.05$
5 mg BID=tofacitinib 5 mg twice daily; 10 mg BID=tofacitinib 10 mg twice daily
For readability, y-axes are different for the different variables.
A3921032 = Step, A3921044 = Scan, A3921046 = Sync, A3921064 = Standard
Non-responder imputation used in analysis

In the 12-month Studies Scan, Sync and Standard, from 45% to 49% of placebo patients were considered nonresponders (i.e. those with less than 20% improvement in swollen and tender joint counts) and were advanced to one of the pre-specified tofacitinib treatments at Month 3. The ACR20 response rates in both the placebo to 5 mg and placebo to 10 mg treatment groups began to increase after Month 3 when nonresponding patients advanced to active treatment, and all groups had similar response rates by Month 9 following advancement of the remaining placebo patients to active treatment at Month 6 (e.g. see Figure 9). ACR response was maintained for the duration of the studies. As an example, Figure 9 shows the ACR50 response rate for the Scan study out to one year. Note that placebo patients rapidly respond after advancing to tofacitinib. Results for 1046/Sync, 1064/Standard were similar to the 1044/Scan study; i.e., placebo patients rapidly respond after advancing to tofacitinib. Similar and consistent trends were also shown for ACR20 and ACR70.

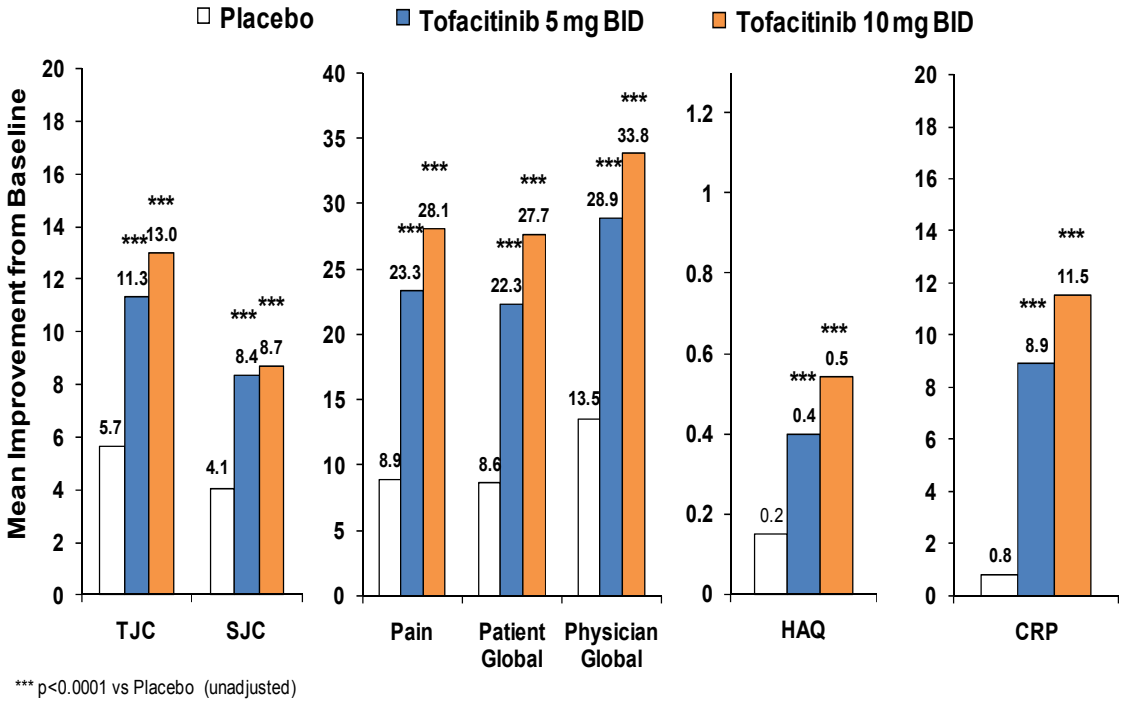
Figure 9. ACR50 Response Rate (%) (±SE) through 12 Months – 1044/Scan Study



PBO = placebo, NR = nonresponder
LOCF imputation used

Each of the components of the ACR assessment was consistently improved from baseline in patients treated with tofacitinib 5 mg or 10 mg BID compared with placebo. Patients assessed the severity of their arthritis pain using a 100 mm visual analog scale (VAS) by placing a mark on the scale between 0 (no pain) and 100 (most severe pain), which corresponded to the magnitude of their pain. In the tofacitinib Phase 3 studies, patient reported pain, was improved (reduced) at 3 months by -23 to -27 mm and -25 to -28 mm for the 5 and 10 mg BID doses, respectively (mean change from baseline). These changes in pain were uniformly superior to placebo. As an example, Figure 10 shows the improvement from baseline in the components of the ACR responder criteria at Month 3 in the Scan study.

Figure 10. Improvement across All ACR Response Components at Month 3, 1044/Scan Study

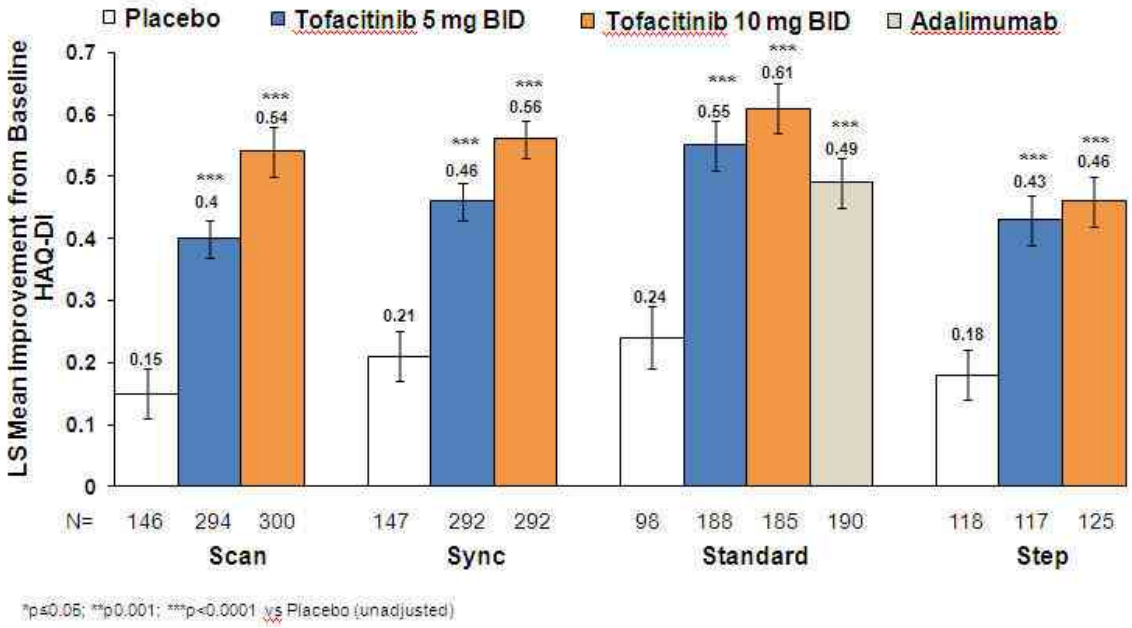


TJC = tender joint count, SJC = swollen joint count, HAQ = health assessment questionnaire, CRP = C-reactive protein

8.10.1.2. Physical Function: Health Assessment Questionnaire-Disability Index (HAQ-DI)

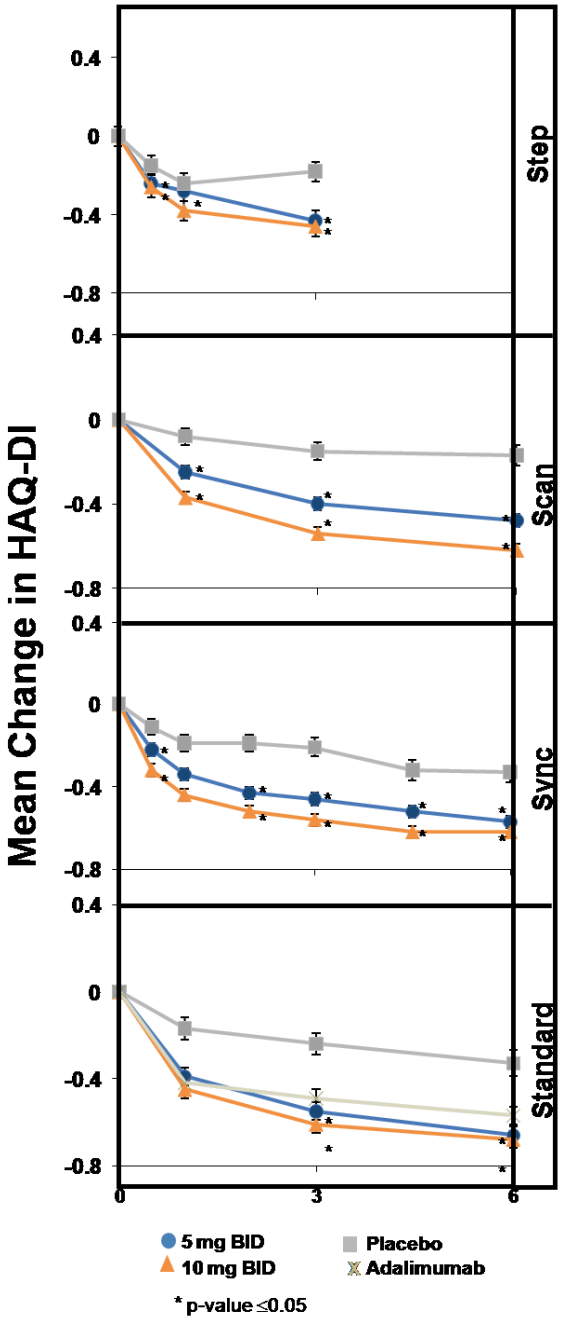
Patients receiving tofacitinib 5 mg and 10 mg BID demonstrated statistically significantly greater improvement from baseline in physical functioning compared with placebo at Month 3 (primary endpoint, Figure 11) and Month 6 in all Phase 3 background DMARD studies. Tofacitinib 5 mg and 10 mg BID treated patients exhibited significantly greater improvements in physical functioning compared with placebo as early as Week 2 (Figure 12), and mean HAQ-DI improvements were maintained to Month 12 in tofacitinib-treated patients. As a representative example, Figure 13 shows the HAQ-DI improvement out to one year for the 1044/Scan study. Note that placebo patients rapidly respond after advancing to tofacitinib.

Figure 11. LS Mean Changes from Baseline in HAQ-DI at Month 3 – Phase 3 Background DMARD Studies



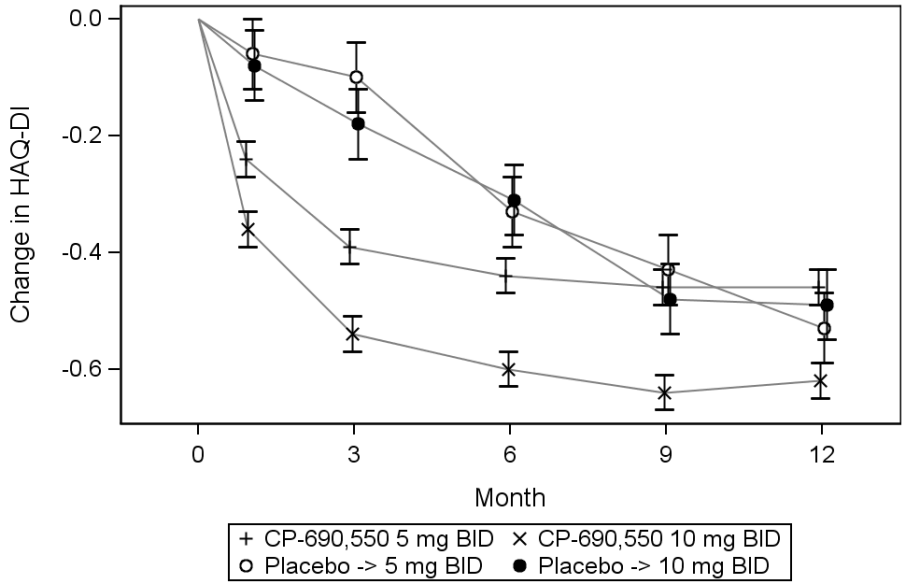
A3921032 = Step, A3921044 = Scan, A3921046 = Sync, A3921064 = Standard

Figure 12. LS Mean Change (±SE) from Baseline in HAQ-DI (Comparison to Placebo) – Background DMARD Studies



5 mg BID=tofacitinib 5 mg twice daily; 10 mg BID=tofacitinib 10 mg twice daily
A3921032 = Step, A3921044 = Scan, A3921046 = Sync, A3921064 = Standard
longitudinal model used for analysis.

Figure 13. LS Mean Changes (±SE) From Baseline in HAQ-DI Through Month 12, 1044/Scan Study (1-Year Analysis)



CP-690,550 = tofacitinib
HAQ-DI values for patients identified as nonresponders at Month 3 were set to missing post Month 3

8.10.1.3. Comparison of ACR Responses and HAQ-DI Changes in Tofacitinib-Treated and Adalimumab-Treated Patients

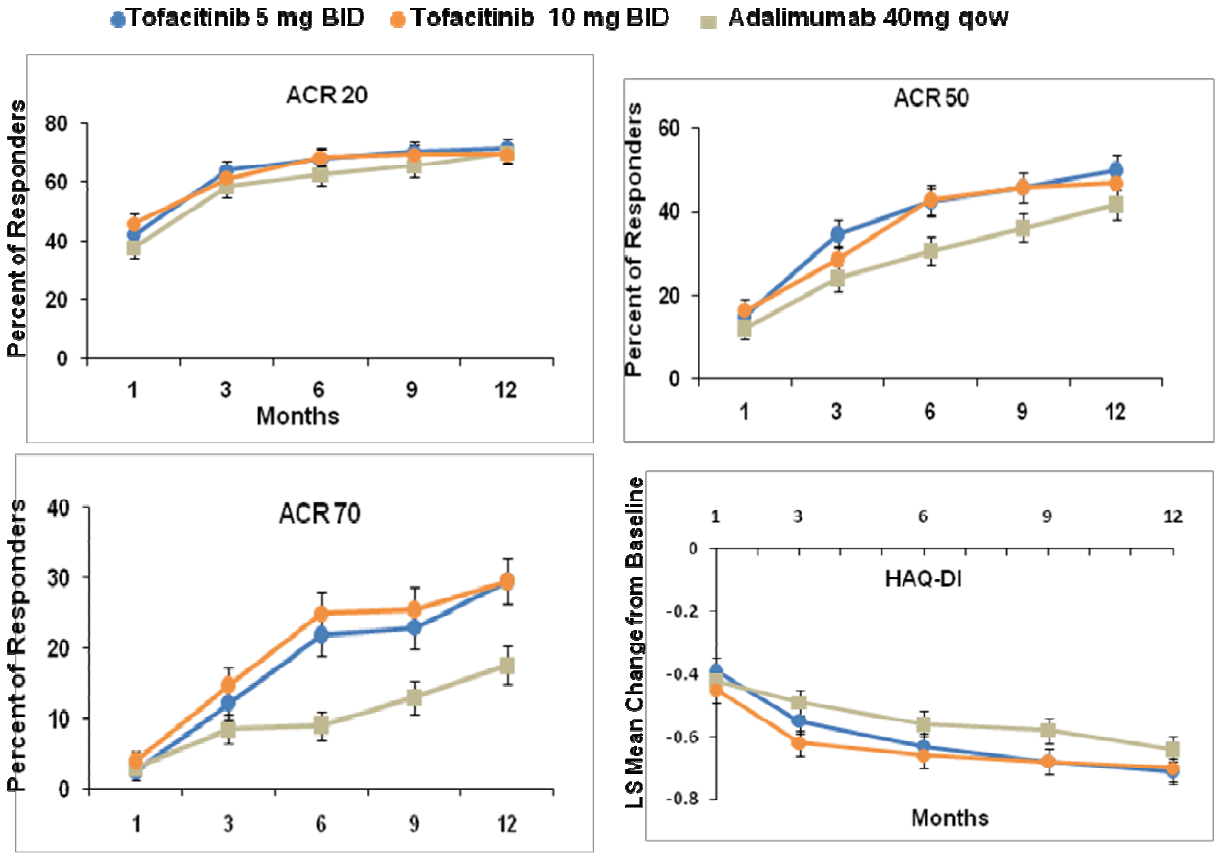
The Standard Study (1064) was a 12-month study in which 717 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX received tofacitinib 5 or 10 mg BID, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX. At the Month 3 visit, non-responding placebo patients were advanced in a blinded fashion to a second predetermined treatment of tofacitinib 5 or 10 mg BID. At the end of Month 6, all placebo patients were advanced to their second predetermined treatment in a blinded fashion.. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6. The efficacy comparisons of tofacitinib to adalimumab were prespecified secondary endpoints in the study.

The proportion of patients achieving ACR20 response in the tofacitinib treatment groups and the adalimumab treatment group at Months 3 or 6 were similar. ACR50 response rates were greater in the tofacitinib 5 mg treatment group than in the adalimumab treatment group at Month 3 (nominal p-value ≤0.05); although the ACR50 response rates were numerically better in both tofacitinib dose groups than in the adalimumab group at Month 6, the differences were not statistically significant. ACR70 response rates were better in both tofacitinib dose groups than in the adalimumab group at Month 6 (nominal p-value ≤0.0019).

Improvements from Baseline at Month 3 and Month 6 in the adalimumab group were less pronounced compared to improvements at the same time points for the tofacitinib doses. Compared with adalimumab-treated patients, patients in the tofacitinib 10 mg BID group had greater decreases from baseline in HAQ-DI at Month 3 (nominal p-value = 0. 016).

ACR20, ACR50, and ACR70 response rates as well as decreases from baseline in HAQ-DI for tofacitinib 5 and 10 mg BID groups and adalimumab group through Month 12 are presented in Figure 14. The ACR20, ACR50, ACR70 response rates and changes from baseline in HAQ-DI were similar or better for tofacitinib 5 mg or 10 mg BID group than that seen for adalimumab group during the entire treatment period.

Figure 14. ACR20, ACR50, ACR70 Response Rates (%) (±SE)and Changes in HAQ-DI (±SE) through Month 12 of Tofacitinib 5 mg and 10 mg BID and Adalimumab 40 mg QOW, 1064/Standard Study



SE = Standard error, QOW = every other week
LOCF imputation

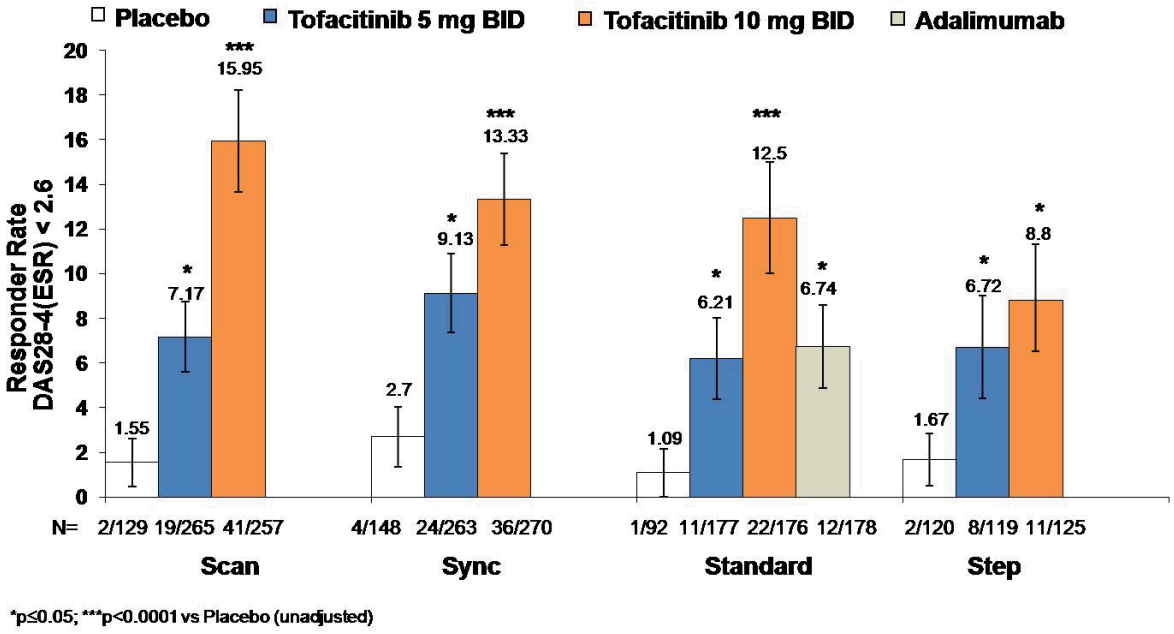
8.10.1.4. Disease Activity Scores

The proportion of patients achieving DAS28-4(ESR) <2.6 at the primary time point was statistically significantly different from the placebo group for both tofacitinib dose groups

across the Phase 3 background DMARD studies (p-value <0.05). The proportions for the tofacitinib 10 mg dose group were notably greater than for the 5 mg dose group (see Figure 15 and Table 11).

The proportion of patients achieving DAS28-4(ESR) <2.6 as well as DAS28-3(CRP) <2.6 (data not shown) at Month 3 was significantly greater with both doses of tofacitinib compared with placebo. The percentage of patients treated with tofacitinib reaching these endpoints increased from Month 3 to Month 6. Statistically significant differences from placebo were demonstrated as early as Month 1 or Month 3, the first assessment time points (Figure 16).

Figure 15. Patients Achieving DAS28-4(ESR) <2.6 at Primary Time Points – Phase 3 Background DMARD Studies



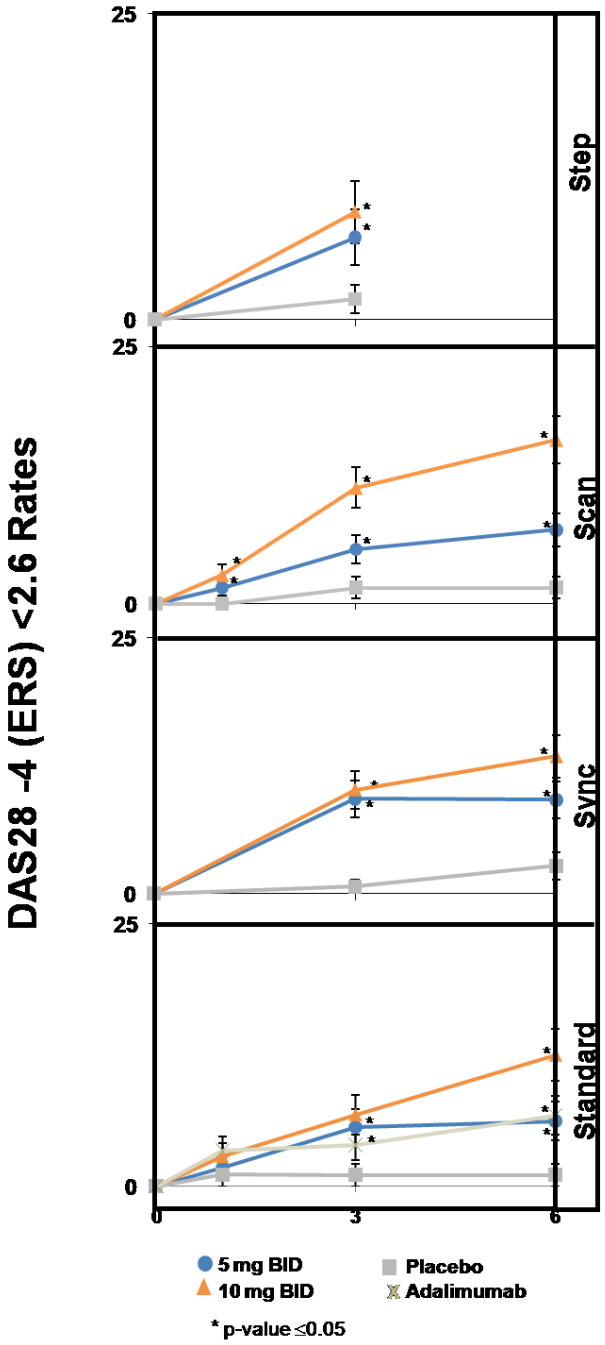
A3921032 = Step, A3921044 = Scan, A3921046 = Sync, A3921064 = Standard
Primary time point is Month 6 for Scan, Sync and Standard studies and Month 3 for the Step study

Table 11. Summary of Patients Achieving DAS28-4(ESR) <2.6 (Comparisons to Placebo) at Primary Time Point – Phase 3 Background DMARD Studies

Treatment	N	n	%	Comparison to Placebo			
				Difference	95% CI for Difference		P- Value
					Lower	Upper	
1044/Scan							
Tofacitinib 5 mg BID	265	19	7.17	5.61	1.85	9.38	0.0034*
Tofacitinib 10 mg BID	257	41	15.95	14.40	9.44	19.36	<0.0001
Placebo	129	2	1.55	Not applicable			
1046/Sync							
Tofacitinib 5 mg BID	263	24	9.13	6.42	2.07	10.77	0.0038
Tofacitinib 10 mg BID	270	36	13.33	10.63	5.80	15.45	<0.0001
Placebo	148	4	2.70	Not applicable			
1064/Standard							
Tofacitinib 5 mg BID	177	11	6.21	5.12	0.98	9.26	0.0151
Tofacitinib 10 mg BID	176	22	12.50	11.41	6.08	16.73	<0.0001
Adalimumab 40 mg q 2 wk	178	12	6.74	5.65	1.40	9.90	0.0091
Placebo	92	1	1.09	Not applicable			
1032/Step							
Tofacitinib 5 mg BID	119	8	6.72	5.05	0.00	10.10	0.0496
Tofacitinib 10 mg BID	125	11	8.80	7.13	1.66	12.60	0.0105
Placebo	120	2	1.67	Not applicable			

BID = twice daily, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, N = number of patients, n = number of patients meeting prespecified criteria, CI = confidence interval,
Primary time point is Month 6 for 1044/Scan, 1046/Sync and 1064/Standard studies and Month 3 for the 1032/Step study
Non-responder imputation appled
*Nominal p-value. Does represent formal statistical inference per statistical analysis plan step down procedure. See Section 8.5.

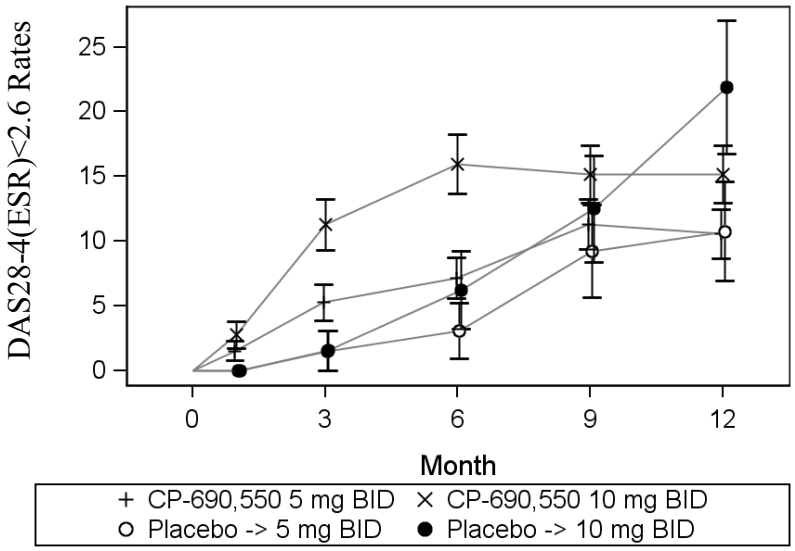
Figure 16. Proportion of Patients Achieving DAS28-4(ESR) <2.6 through Primary Time Point – Phase 3 Background DMARD Studies



5 mg BID=tofacitinib 5 mg twice daily; 10 mg BID=tofacitinib 10 mg twice daily
A3921032 = Step, A3921044 = Scan, A3921046 = Sync, A3921064 = Standard
NRI applied, comparison to placebo

DAS28-4(ESR) <2.6 response was maintained for the duration of the studies. As a representative example, Figure 17 shows the DAS28-4(ESR) <2.6 response rate for the Scan study out to one year. As with the other endpoints, placebo patients rapidly respond after advancing to tofacitinib.

Figure 17. Rates (%) of Patients Achieving DAS28-4(ESR) <2.6 Response through Month 12 (±SE), 1044/Scan Study



CP-690,550 = tofacitinib

8.10.1.5. Inhibition of the Progression of Structural Damage: Modified Total Sharp Score (mTSS)

The inhibition of progression of structural damage was assessed on stable background methotrexate treatment in the 1044/Scan study. With the need to minimize duration of patient exposure to placebo treatment to no greater than 6 months, at the Month 3 visit, non-responding placebo patients were advanced in a blinded fashion to a second predetermined treatment of tofacitinib 5 or 10 mg BID, and at the end of Month 6, all placebo patients were advanced to their second predetermined treatment in a blinded fashion. Total Sharp Scores at Month 6 is one of the 4 co-primary endpoints in the study.

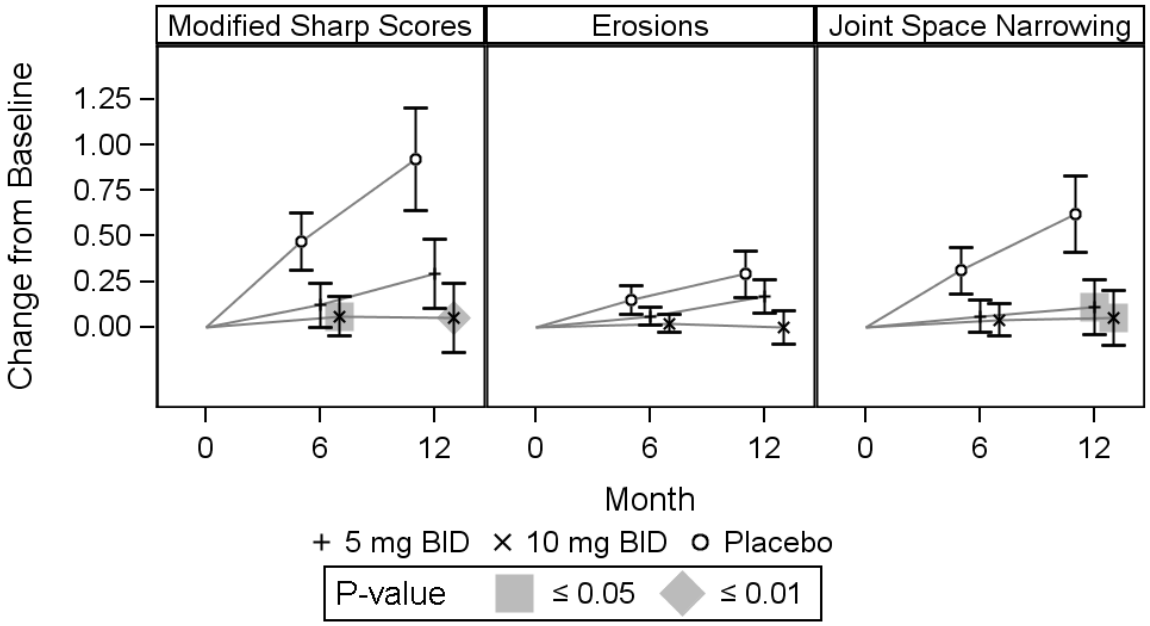
Treatment groups were balanced with respect to the baseline degree of damage shown on x-ray image and the estimated annual rate of progression of mTSS (4.8 to 5.5 unit/year).

Tofacitinib inhibited the progression of structural damage as measured by change from baseline in mTSS at the 6-month primary time point. Differences from placebo in the mean changes from baseline in mTSS at Month 6 (primary endpoint) were -0.34 (95% CI: -0.73, 0.04) and -0.40 (95% CI: -0.79, -0.02) in the tofacitinib 5 mg and 10 mg BID treatment groups, respectively. The mean change in mTSS represents an approximately 74 and 87% reductions for the 5 and 10 mg tofacitinib doses, respectively, relative to the change for placebo. The difference was statistically significant for the 10 mg dose (p = 0.0376); but not for the 5 mg dose (p = 0.0792).

The difference from placebo group at Month 12 was also statistically significant for the 10 mg BID dose group (p = 0.0081) but was not statistically significant for the 5 mg BID

dose group (p= 0.0558). Mean changes from baseline in mTSS, erosion score, and JSN score are presented in Figure 18.

Figure 18. LS Mean Changes (±SE) From Baseline in van der Heijde Modified Total Sharp Score, Erosion Score, and Joint Space Narrowing Score through Month 12 (Comparisons to Placebo, 1-Year Analysis), 1044/Scan Study

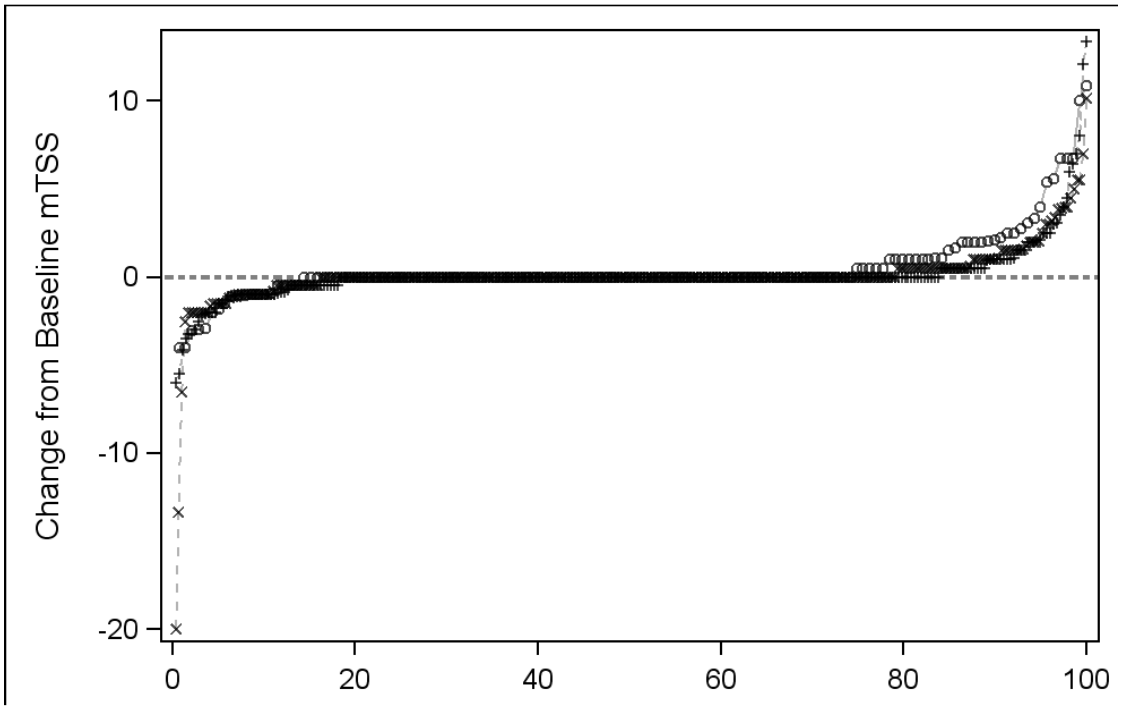


Treatment with tofacitinib doses of both 5 mg or 10 mg BID resulted in less progression from baseline in the two components of the mTSS (joint space narrowing (JSN) and erosion scores) compared with placebo at both Months 6 and 12. The small change in erosion scores in the placebo patients was likely influenced by nonresponding placebo patients (approximately 50%) advancing to active treatment with tofacitinib at Month 3. One consequence of this advancement was the limited duration of direct placebo comparisons, a particular issue for radiographic outcomes, where effects may not be measurable for months after a beneficial intervention. The primary outcome of change from baseline in mTSS was measured at Month 6, and the placebo group at that time included patients who had already advanced to tofacitinib treatment 3 months prior.

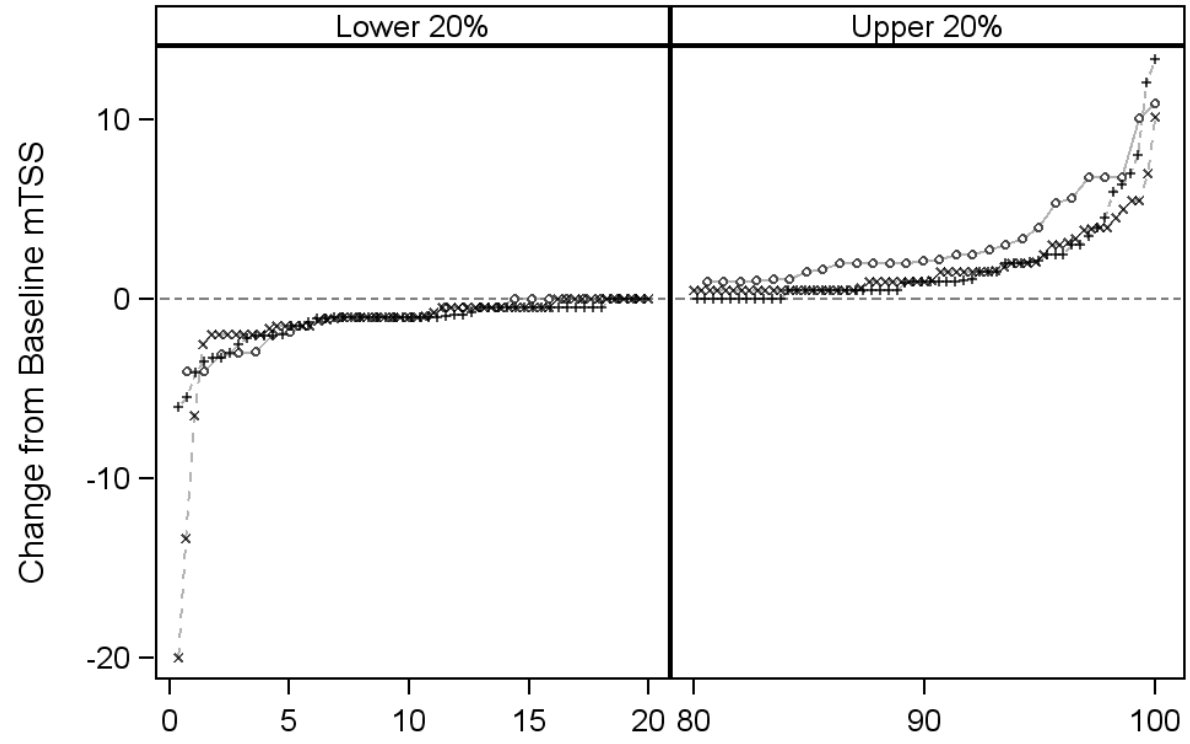
To show the distribution of mTSS changes for the population as a whole, the changes from baseline in mTSS were computed for each patient, and the individual values arranged according to their rank in cumulative probability plots for Month 6 and Month 12 in Figure 19; the lower 20% and upper 20% were also shown in magnified scale. These cumulative distribution plots for the tofacitinib 5 mg BID and 10 mg BID groups were very similar to one another and different from the plots for the placebo group. These plots show that fewer tofacitinib-treated patients for both the 5 and 10 mg BID dose had increased joint damage relative to placebo-treated patients and that the cumulative damage represented by the area under the curve on the right is greater for placebo than for tofacitinib.

Figure 19. Cumulative Probability of Changes from Baseline to Months 6 and 12 in mTSS (LEP, Comparisons to Placebo, 1044/Scan Study (1-Year Analysis)

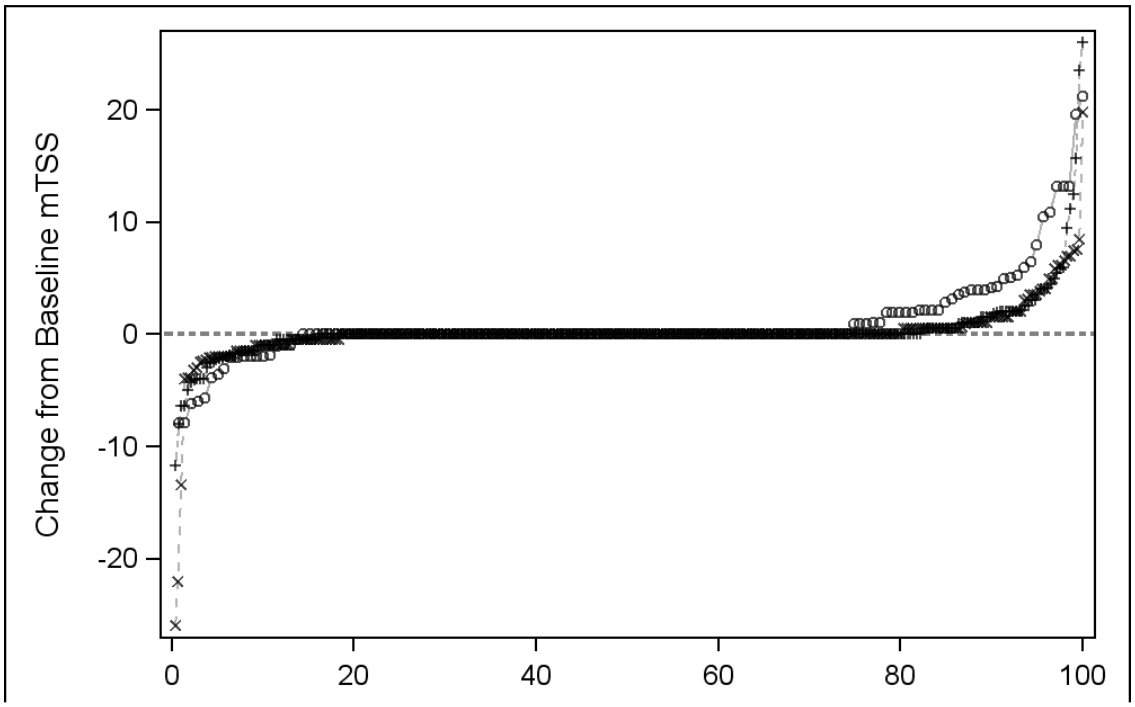
Month 6



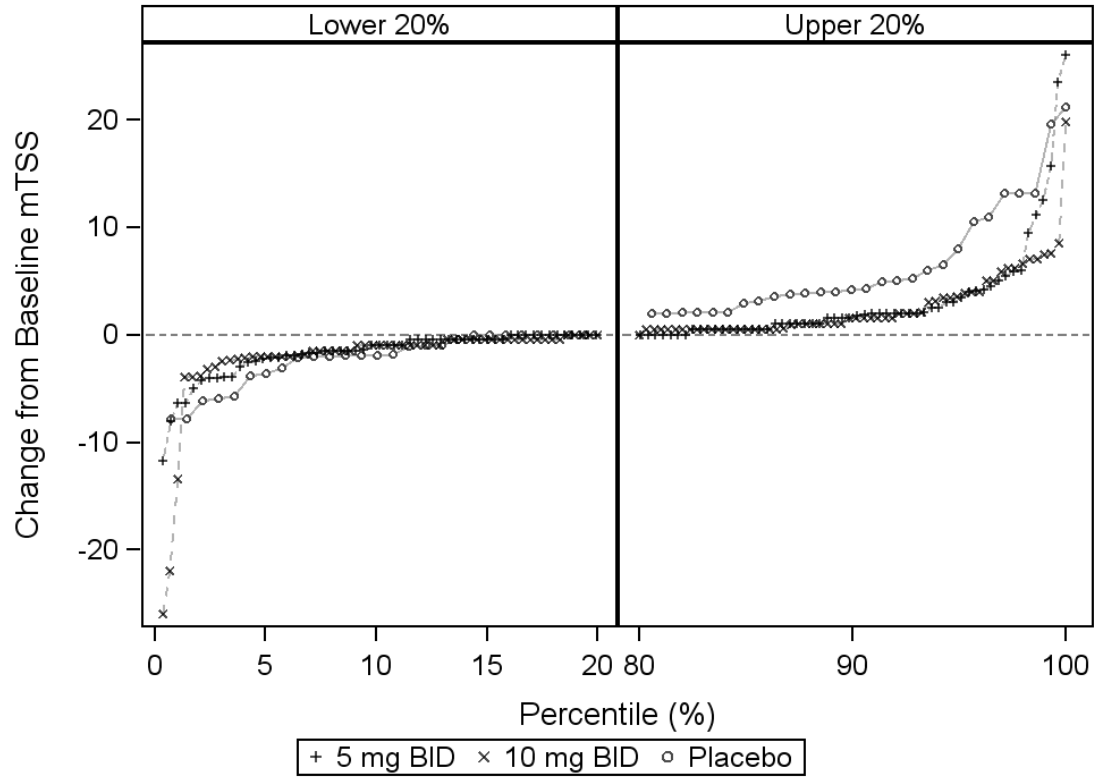
Magnified Scale



Month 12



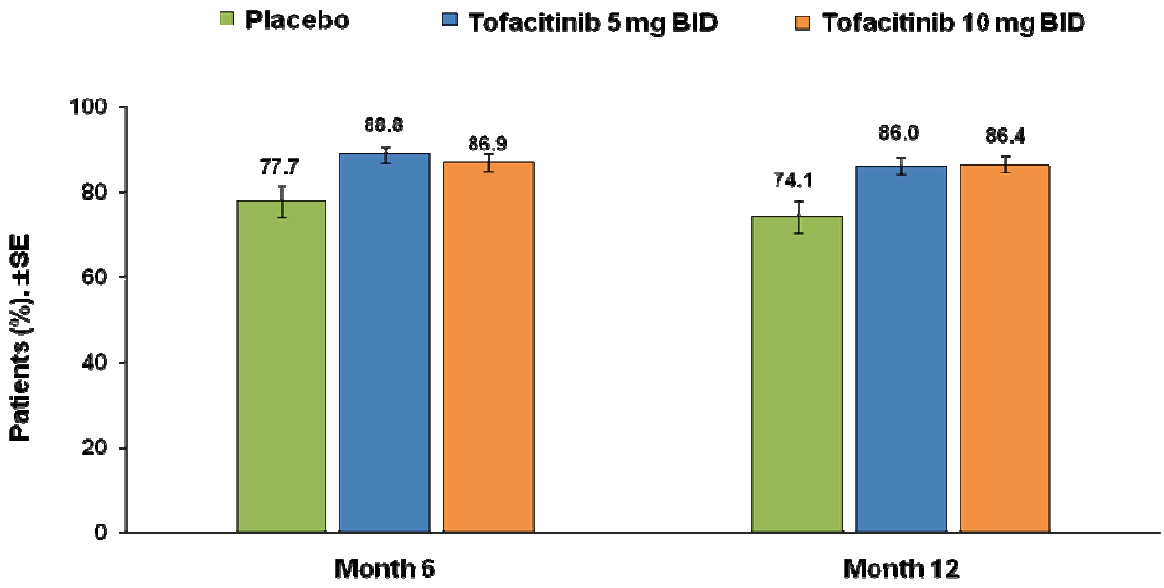
Magnified Scale



BID=twice daily, LEP=linear extrapolation, mTSS=modified Total Sharp score

The proportion of patients with no radiographic progression (defined as ≤0.5 unit increase from baseline in mTSS) at both Months 6 and 12 was significantly greater in both the tofacitinib 5 mg and 10 mg BID groups compared with placebo; the proportion of patients was also similar in both 5 and 10 mg BID treatment groups (nominal p-values ≤0.023); (Figure 20).

Figure 20. Proportion of Patients (%)(±SE) with No Progression in mTSS through Month 12 , 1044/Scan Study (1-Year Analysis)



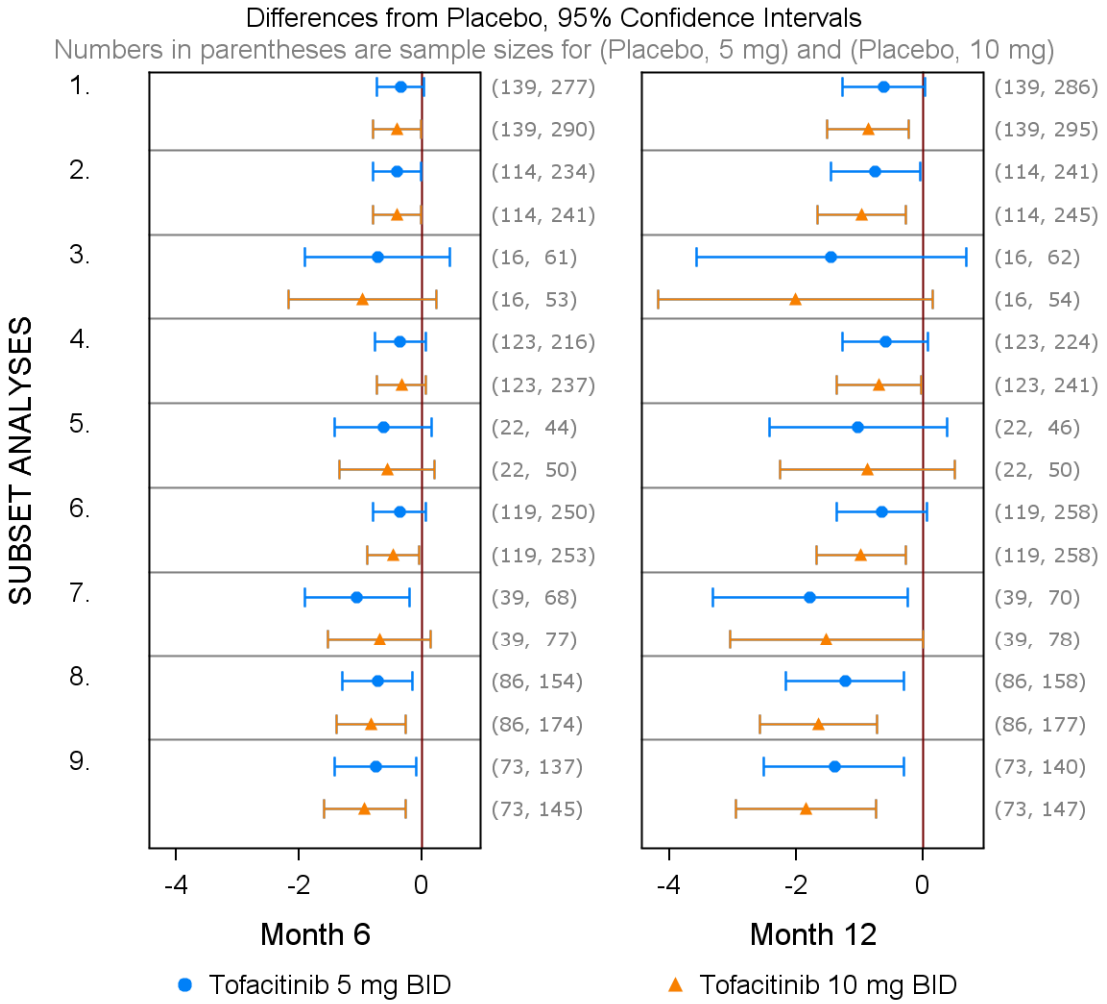
*p-value <0.05, **p-value <0.01 vs placebo
mTSSΔ ≤0.05
Comparisons to Placebo

The 1044/Scan study was powered to test the hypothesis of a significant difference in the mean mTSS change from baseline between tofacitinib and placebo treated patients at Month 6. Based on published literature reviewed during the design of the study, the sponsor assumed that the placebo group would have a mean increase (deterioration) from baseline of at least 1.4 units and the observed difference between tofacitinib and placebo would be at least 0.8 units. However, the observed change from baseline in mean mTSS for the placebo group at Month 6, which placed an upper limit on the observable difference, was only 0.47 units, with both tofacitinib arms showing negligible increases (0.06 and 0.12 units) from baseline. The change in the placebo arm over 6 months was also approximately one fifth of that predicted from the estimated mean annual radiographic progression at baseline of 4.8 units/year in the placebo group and was significantly less than the progression of radiographic joint damage expected in DMARD-IR populations based on a meta analysis performed by the sponsor of 44 published studies. These findings are also consistent with the reported trend towards decreased disease progression in RA patients over time, attributable to improved treatment options (Finckh, 2006-1, Finckh, 2006-2, Rahman, 2011) as opposed to minimal treatment (in the meta analysis referred above) or prior standard of care treatment and, combined with the need to minimize duration of patient exposure to placebo treatment

to no greater than 6 months, made the demonstration of a structural benefit more challenging in the 1044/Scan study.

Despite the limited degree of joint damage progression observed in the entire study population, more pronounced treatment effects were observed for the 5 and 10 mg BID tofacitinib treatment groups in post-hoc analyses of the subset of patients with prognostic factors predictive of greater progression of joint damage (so called “poor prognostic factors”) with greater differences from placebo for the tofacitinib doses in the subgroup of patients exhibiting poor prognostic factors (Figure 21).

Figure 21. Differences from Placebo in Mean Changes from Baseline at Months 6 and 12 in mTSS with 95% CI, 1044/Scan Study (Subset Analyses, 1-Year Analysis)



SUBSET ANALYSES

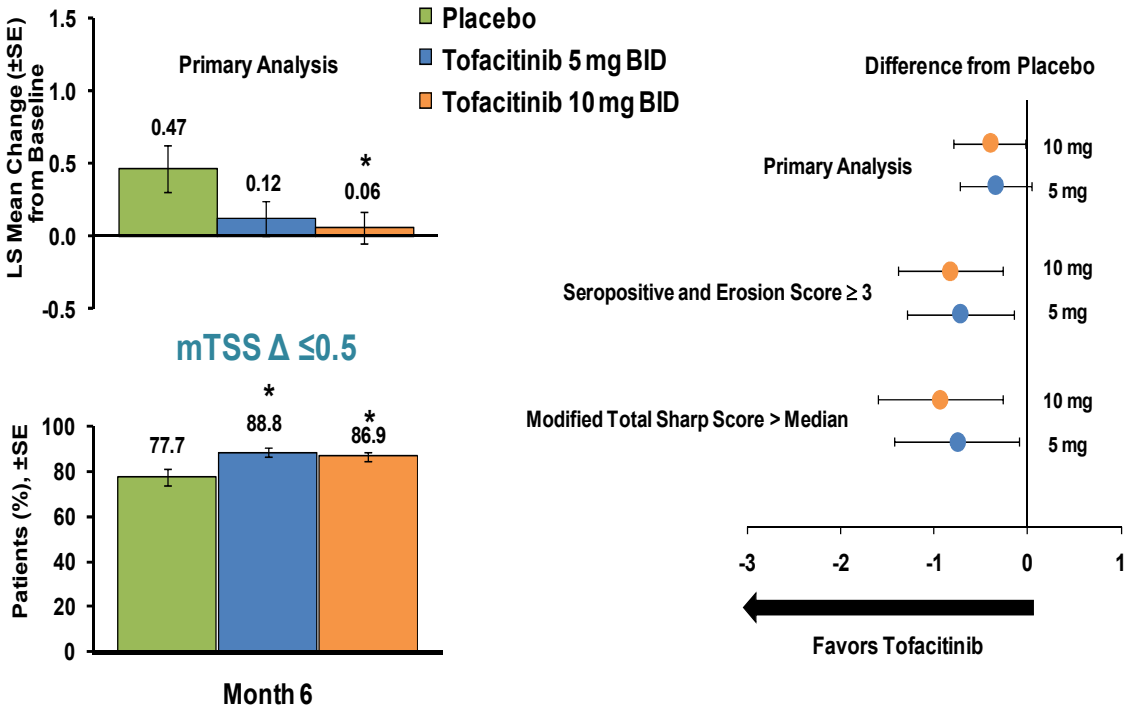
1. Primary
2. Anti-CCP +
3. Prior Biologic DMARD Exposure (Yes)
4. Prior Traditional DMARD Exposure (Yes)
5. Disease Duration < 2 years
6. DAS28-4(ESR) > 5.1
7. Annual Radiographic Progression ≥ 5
8. Seropositive and Erosion Score ≥ 3
9. Baseline mTSS > Median

(Subsets 2-9 are based on baseline status.)

Despite the less than expected structural progression in the placebo group and limited duration of placebo exposure (3 or 6 months), which constrained the demonstration of tofacitinib treatment benefit in inhibiting radiographic structural damage, the totality of radiographic data show that both 10 mg and 5 mg BID doses inhibit the progression of

structural damage as previously described; outside of the statistical significance of the pre-specified primary structural endpoint, differences between the 5 and 10 mg BID doses were minimal across the various methods to assess radiographic progression (Figure 22).

Figure 22. Summary of mTSS Radiographic Progression Assessments (Month 6), 1044/Scan Study



*p-value ≤0.05

8.10.2. Efficacy Results for Monotherapy Studies

Efficacy of tofacitinib 5 mg and 10 mg BID given as monotherapy for the treatment of RA in patients having an inadequate response to ≥1 DMARD treatment was assessed in the Phase 3 1045/Solo study.

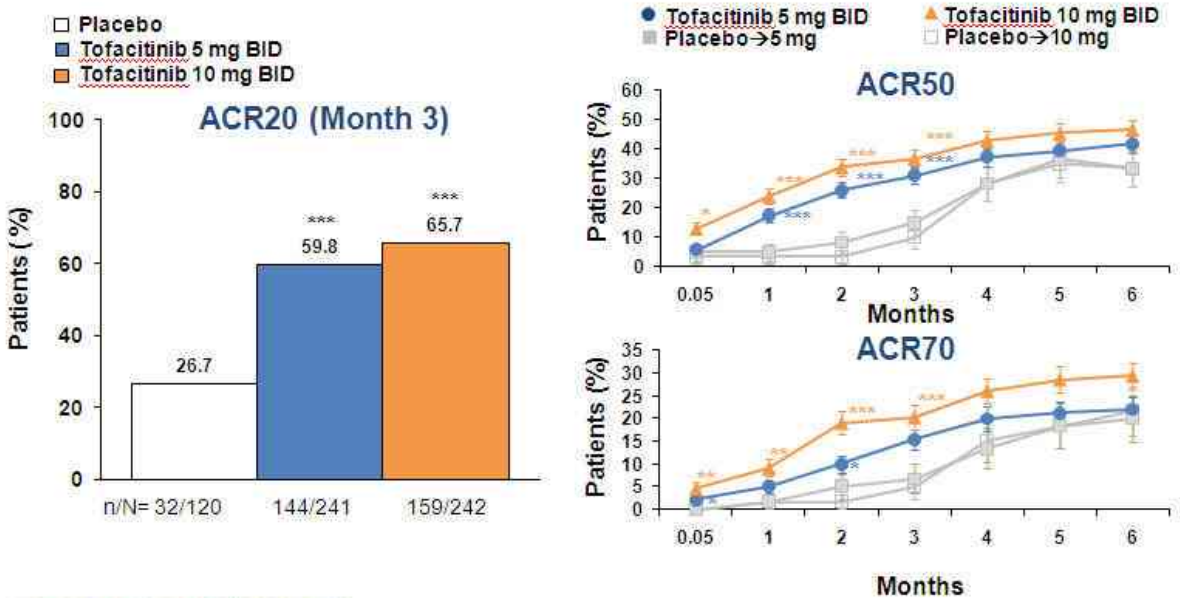
8.10.2.1. Signs and Symptoms: ACR Responses in Monotherapy 1045/Solo Study

Both tofacitinib 5 mg and 10 mg treatment groups demonstrated statistically significant and clinically meaningful reductions in signs and symptoms of RA over placebo for the primary endpoint of ACR20 response at Month 3 in the monotherapy Solo study (Figure 23).

ACR20 efficacy response was observed starting at Week 2 and was maintained through the duration of the study. The nominal p-values for the comparisons of tofacitinib with placebo

were consistently <0.05 for all post baseline evaluation time points starting at Week 2 through the placebo-controlled period.

Figure 23. ACR20, ACR50, ACR70 Response Rate (%) (NRI, Comparisons to Placebo), 1045/Solo Study



*p-value ≤0.05, **p-value <0.01, ***p-value <0.0001

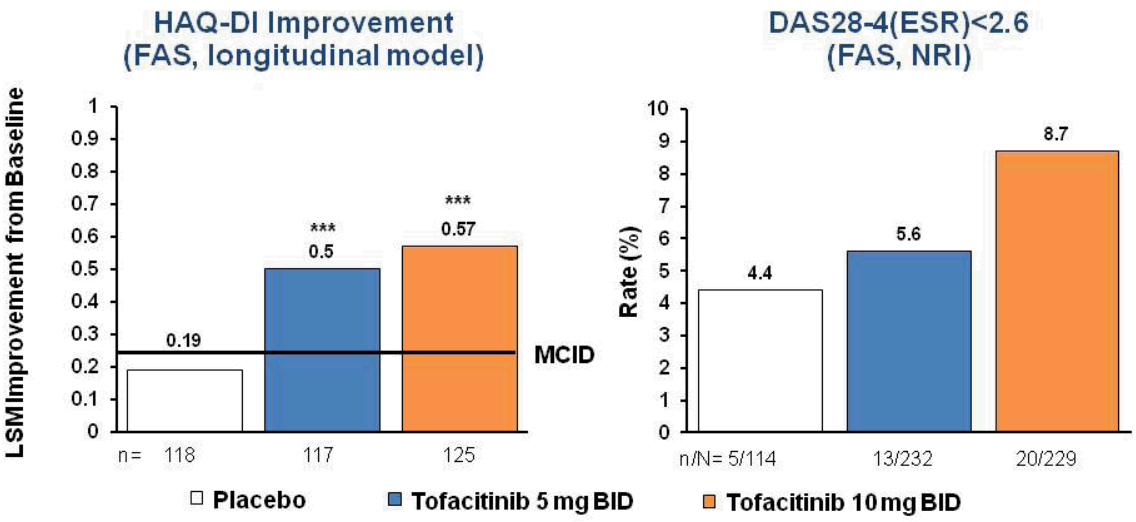
As in the background DMARD studies, results of ACR50 and ACR70 responses were consistent with the ACR20 results in the 1045/Solo study; ACR50 and ACR70 responses were consistently greater in the tofacitinib treatment groups compared with the placebo group. ACR50 and ACR70 responses are presented in Figure 23. The nominal p-values for the comparisons with placebo were consistently <0.05 for both tofacitinib dose groups starting at Week 2 onward. ACR20, ACR50 and ACR70 responses were numerically higher in the 10 mg tofacitinib group compared with the 5 mg group at all post baseline evaluation time points; the differences between the 5 mg and 10 mg BID groups were most pronounced for ACR70.

8.10.2.2. Physical Function: Health Assessment Questionnaire-Disability Index (HAQ-DI) and Disease Activity Scores in Phase 3 Monotherapy 1045/Solo Study

Compared with placebo, statistically significant decreases in HAQ-DI at Month 3 were observed in both the tofacitinib 5 mg and 10 mg BID treatment groups in the Phase 3 monotherapy study. The differences from placebo were similar between the 5 mg and 10 mg dose groups, although the 10 mg dose group had numerically greater decrease than the 5 mg dose group (Figure 24).

Responses for both the tofacitinib 5 and 10 mg doses were superior to placebo at Week 2 and onward.

Figure 24. Improvement in HAQ-DI and DAS28-4(ESR) <2.6 Response, Monotherapy 1045/Solo Study



*p≤0.05; ***p<0.0001 vs PBO at Month 3 (unadjusted)
LSM= least squares mean; MCID=minimum clinically important difference

Compared with the placebo group, the proportion of patients achieving DAS28-4(ESR) <2.6 at Month 3 was numerically but not statistically significantly greater for both tofacitinib dose groups in the Phase 3 monotherapy Study 1045/Solo (Figure 24). The proportion of patients in the 10 mg dose group was numerically greater than the 5 mg dose group.

8.10.3. Health-Related Quality of Life: SF-36 Health Survey

The measurement of health-related quality of life entails individuals' evaluation of their own health status by self-reported survey instruments and provides an important way to assess whether improvement in clinical measurements translates into recognizable benefits to patients. For these reasons, both the FDA and the EMA have recommended that health-related quality of life be assessed as supporting evidence of efficacy in RA clinical trials. The SF-36v2™ Health Survey was used to assess improvement in health-related quality of life (Ware, 1993).

Significant improvement in all SF-36 domains (Figure 25), as well as the Physical Component Score (PCS) and Mental Component Score (MCS) (Figure 26), were observed, with greater proportions achieving minimum clinically important difference (MCID) with tofacitinib 10 mg than 5 mg in the 4 background DMARD studies; adalimumab demonstrated similar benefits with tofacitinib 5 mg, and tofacitinib 10 mg demonstrated greater benefit than adalimumab in all 8 domains as well as PCS and MCS in the 1064/Standard study.

Figure 25. Difference from Placebo in Mean Change from Baseline in SF-36 Domain Scores at Month 3 with 95% CI – Background DMARD Studies

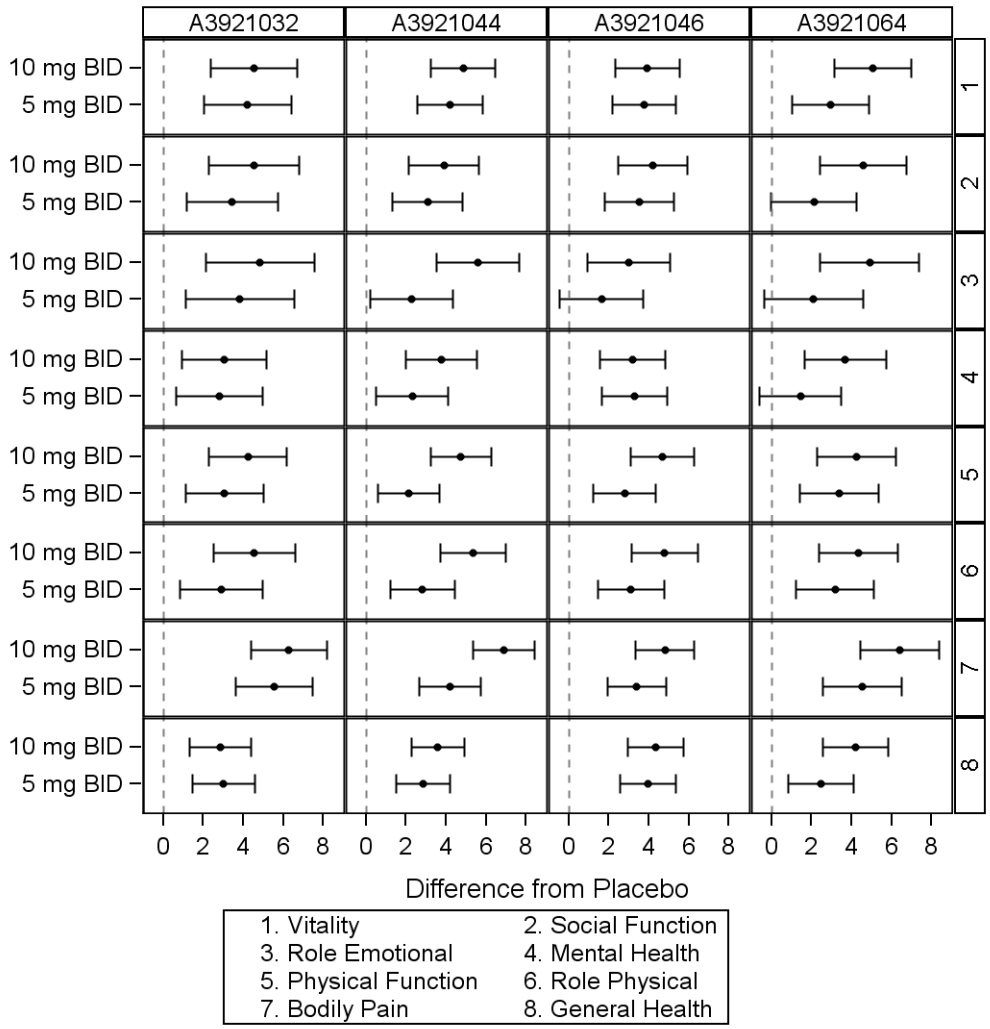
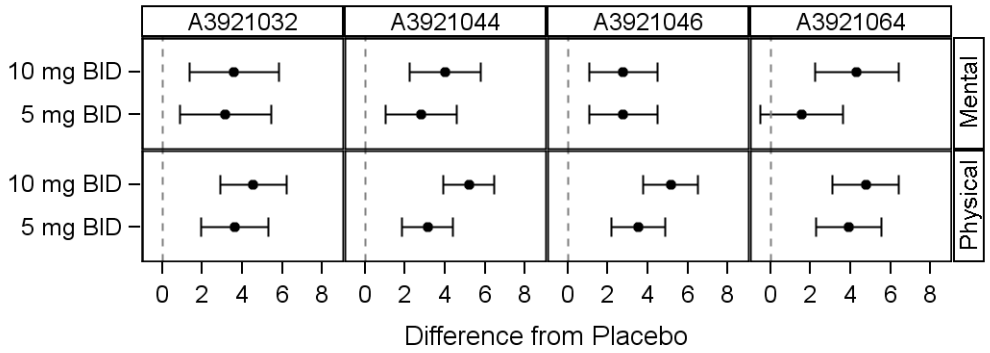


Figure 26. Difference from Placebo in Mean Change from Baseline in SF-36 Component Scores at Month 3 with 95% Confidence Interval – Background DMARD Studies



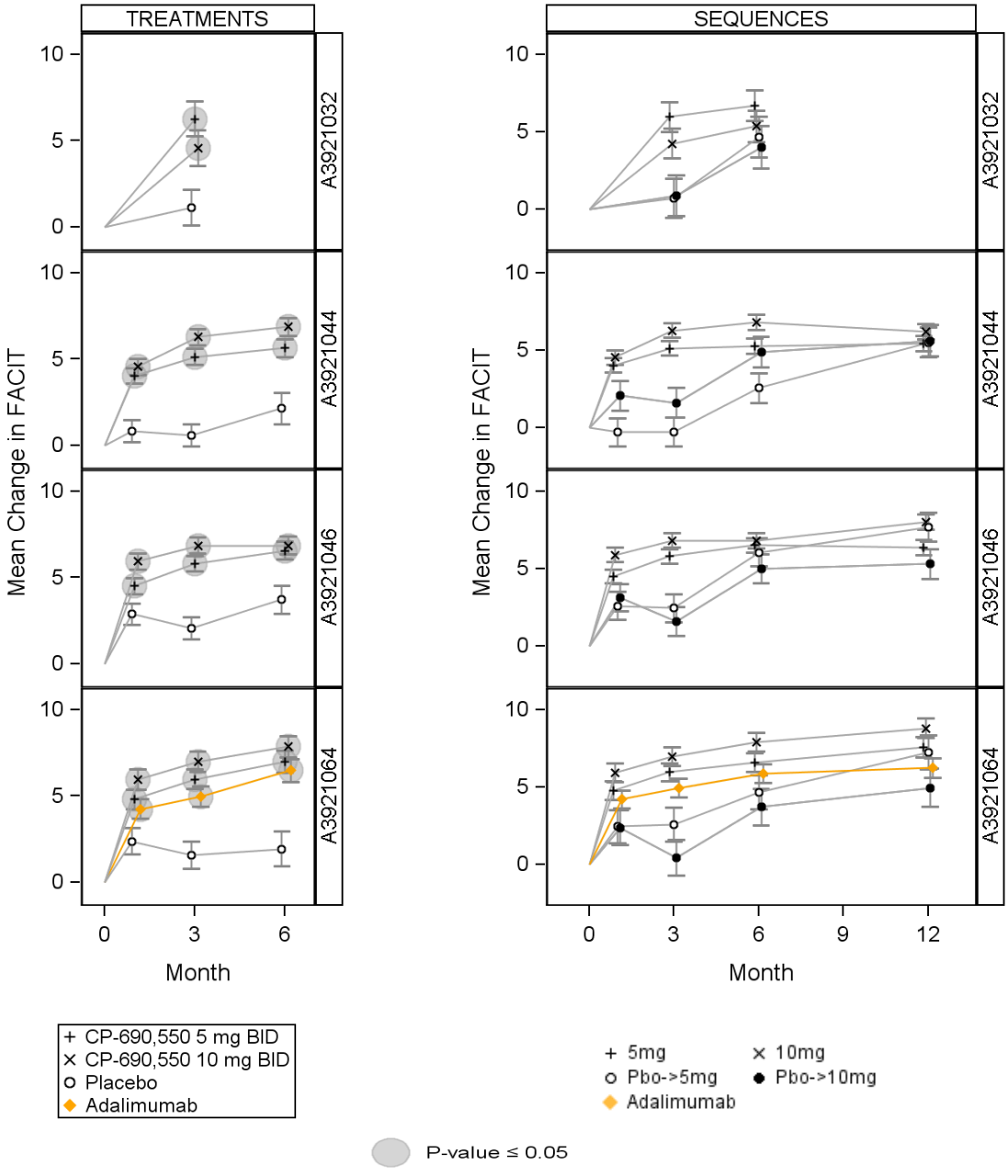
Compared with placebo, a significantly greater percentage of patients treated with tofacitinib 10 mg BID or, with few exceptions, 5 mg BID experienced a MCID (MCID = 5 for domains and 2.5 for PCS and MCS) from baseline at Month 3 in all domains and summary scores in 1044/Scan, 1046/Sync, and 1064/Standard studies.

8.10.4. Fatigue: FACIT Fatigue Scale

Fatigue is a major symptomatic manifestation of RA with studies indicating that its prevalence among RA patients is over 80%, and that fatigue reaches clinically important levels in nearly half of RA patients (Wolfe, 1996). The recognition of fatigue as an important treatment outcome has prompted the European League Against Rheumatism (EULAR) and the ACR expert panels to add fatigue to the core set of recommended endpoints for RA clinical trials.

Changes in fatigue were assessed by the FACIT – F scale at Month 3 in all studies. In all Phase 3 studies, patients receiving tofacitinib 5 and 10 mg BID demonstrated statistically significant and clinically meaningful improvement from baseline in fatigue compared to placebo-treated patients, with statistically significant differences apparent as early as Month 1. In Studies 1044/Scan, 1046/Sync, and 1064/Standard, mean FACIT-F improvements were maintained to Month 12 in tofacitinib-treated patients (Figure 27).

Figure 27. Mean Change from Baseline in FACIT Fatigue Scale through Month 12 (Comparison to Placebo and Comparisons within Sequence) – Background DMARD Studies



CP-690,550 = tofacitinib

A significantly greater percentage of tofacitinib treated patients experienced a minimum clinically important improvement in fatigue (at least 4 units change from baseline on the FACIT-F) at Month 3 compared to patients receiving placebo in 1044/Scan, 1045/Solo, 1046/Sync, and 1064/Standard studies.

8.10.5. Treatment Effect and Subpopulation Analyses

Analysis of the pooled population provides an overall description and estimate of the treatment effect of tofacitinib when given as monotherapy or in combination with nonbiologic DMARDs. Analyses based upon a pooled data set are more robust assessments of differences between treatment groups, and pooled analysis is required for evaluations of response of subpopulations to tofacitinib 5 and 10 mg BID.

Methods of Analysis

Data was pooled and analyzed from nine Phase 2 and Phase 3 studies ≥3 months in duration (monotherapy Studies A3921035, 1040, 1045/Solo and background DMARD Studies A3921025, 1039, 1032/Step, 1044/Scan, 1046/Sync, 1064/Standard). Endpoints of ACR20, 50, 70 response and change from baseline in HAQ-DI (of ≥0.22 improvement) at Month 3 were assessed by baseline demography, baseline disease characteristics, concomitant treatment with DMARDs, and prior RA treatment with nonbiologic DMARDs and biologic DMARDs (categorized as either TNF inhibitors or Non-TNF inhibitors).

Overall Results

No notable differences in tofacitinib efficacy, as assessed by ACR20, ACR50, ACR70 responses, and mean change from baseline in HAQ-DI at Month 3, were found when analyzed by baseline demographic factors, baseline diseases characteristics, concomitant RA medications, and prior RA treatment received, using the pooled Phase 2 and 3 data.

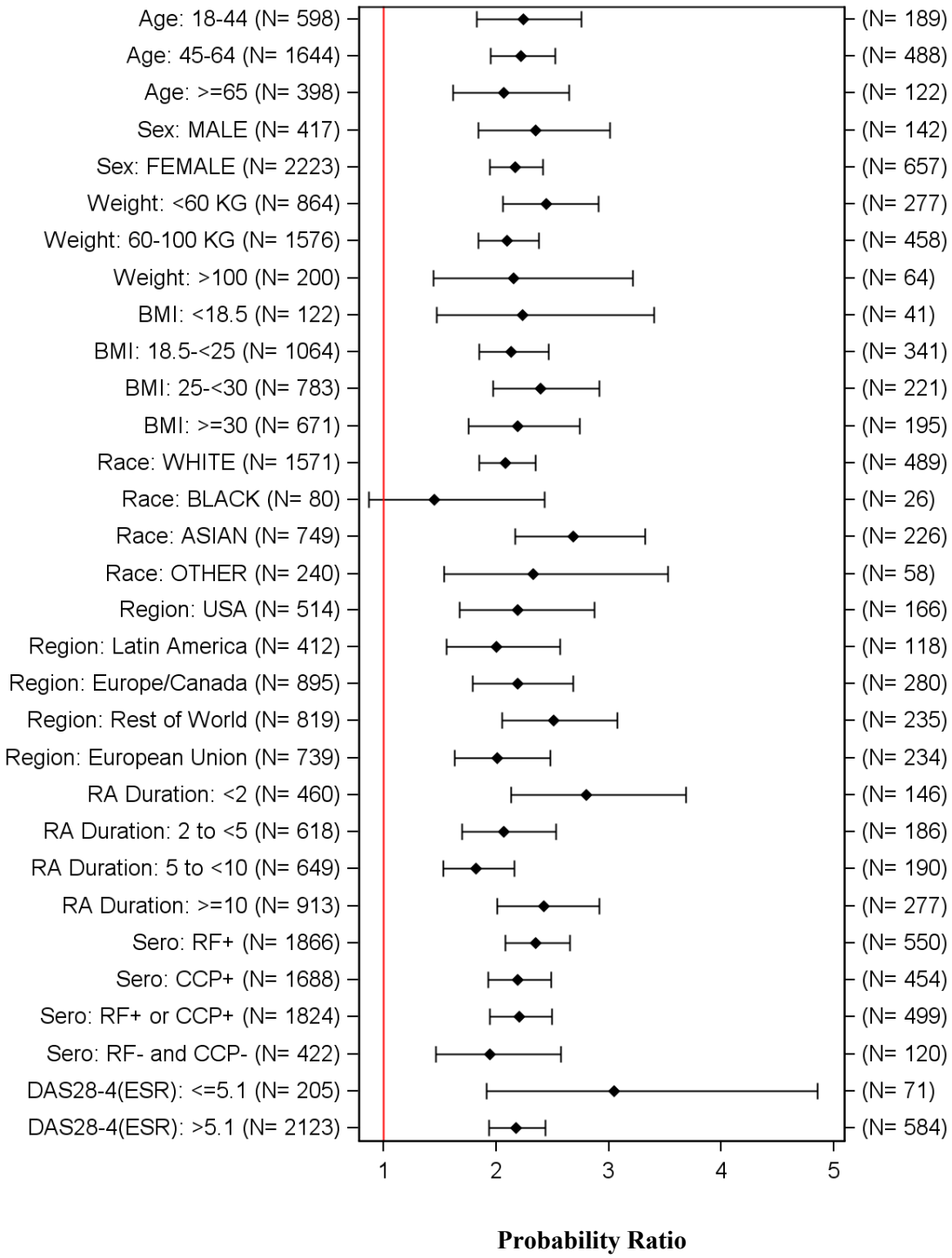
8.10.5.1. Baseline Demographic and Disease Characteristics

Tofacitinib appeared to be equally effective in reducing signs and symptoms of RA compared to placebo in all subgroups evaluated. No notable differences in tofacitinib efficacy were found among subgroups defined by baseline demographic factors such as gender, age, weight, BMI, race, region, and baseline disease characteristics such as RA duration, serological status, DAS28-4(ESR) value, tender joint count, swollen joint count, HAQ-DI score, and corticosteroid use.

The probability ratios (calculated as the ratio of the proportion of responders between tofacitinib and placebo) and, with few exceptions, the 95% CIs of the probability ratios were all greater than 1, with overlapping CIs among the subsets of each characteristic assessed for ACR20 (Figure 28), ACR50, and ACR70 responses, and improvement in HAQ-DI ≥0.22 for the comparisons of tofacitinib 5 mg and 10 mg BID dose groups combined against placebo. The comparisons of individual tofacitinib 5 mg or 10 mg BID dose groups against placebo are consistent with that observed for the dose groups combined.

Asians appeared to have higher tofacitinib treatment-related ACR responses relative to placebo than white or black patients. The response rates in blacks appeared to be lower than the other race groups, and may be related to the small sample size (~3% of the study population) and possibly, greater baseline disease severity and higher body mass.

Figure 28. ACR20 Probability Ratio (of Reaching ACR20 (Primary Outcome) between Tofacitinib and Placebo with 95% CI – Pooled Phase 2 and Phase 3 Studies



N for the left vertical axis is tofacitinib combined sample size. N for the right vertical axis is placebo sample size

8.10.5.2. Concomitant Treatment

ACR Responses by Concomitant DMARDs

The proportion of patients achieving an ACR20 response was similar whether patients were treated with tofacitinib 5 mg or 10 mg BID as monotherapy or on a background DMARD. The responses were also similar in patients who received background MTX, leflunomide, or combinations of DMARDs containing MTX and/or leflunomide. A similar pattern of responses was also observed for ACR50 and ACR70 responses.

HAQ-DI Values by Concomitant DMARDs

The differences from placebo in LS mean changes from baseline HAQ-DI values were numerically greater in the monotherapy studies than background DMARD studies. In background DMARD studies, similar differences from placebo in LS mean decreases in HAQ-DI values from baseline were observed in patients who received background MTX, leflunomide, or combinations of DMARDs containing MTX and/or leflunomide.

8.10.5.2.1. Prior Treatment for Rheumatoid Arthritis

8.10.5.3. Prior Treatment with Nonbiologic DMARDs

In both the monotherapy studies and background DMARD studies, the proportion of patients achieving ACR20, ACR50, and ACR70, and LS mean changes from baseline in HAQ-DI values were similar in patients treated with tofacitinib, irrespective of the number of prior nonbiologic DMARD treatments received.

Prior Treatment with Biologic DMARDs

Tofacitinib was efficacious in patients previously treated with TNF inhibitors. The most direct evidence supporting efficacy in this population is provided by the 1032/Step study, a 6-month Phase 3 study in which patients who had an inadequate response to at least one approved TNF-inhibitor received tofacitinib or placebo added to background MTX. In this study, statistically significant differences from placebo for both 5 mg and 10 mg tofacitinib dose groups were observed across primary and secondary endpoints. As expected for this "difficult to treat" RA population, the observed efficacy tended to be lower than that observed in the other Phase 3 background DMARD studies that enrolled patient populations that were largely biologic DMARD naïve.

The proportion of patients with prior TNF inhibitor experience who participated in Phase 3 studies other than Step ranged from 6.6% to 15.9% in the Phase 3 background DMARD studies and 16.2% in the Phase 3 monotherapy study 1045. The somewhat lower efficacy in patients with prior TNF inhibitor experience relative to TNF inhibitor-naïve patients is also apparent in the combined Phase 2 and Phase 3 data. The difference between TNF inhibitor-naïve patients and those with previous TNF inhibitor treatment experience was less for ACR50 and ACR70 responses compared with ACR20 responses. There did not appear to be a difference in tofacitinib efficacy between patients previously treated with one TNF inhibitor relative to those patients previously treated with more than one TNF inhibitor. The

majority of monotherapy and background DMARD patients participating in the tofacitinib RA studies who had discontinued treatment with a previously administered TNF inhibitor did so due to lack of efficacy as opposed to intolerance (or both lack of efficacy and intolerance). In the small subset (approximately 10%) of patients who had discontinued previous TNF inhibitor treatment due to intolerance in the background DMARD studies, the proportion of patients achieving an ACR response with tofacitinib treatment was similar to that of patients (approximately 50%) who discontinued TNF inhibitor treatment due to lack of efficacy.

Nominal statistical significance in differences from placebo in LS mean change from baseline in HAQ-DI in patients treated with tofacitinib were observed irrespective of the number (0 to 2) of prior TNF inhibitor treatments received in the background DMARD studies. For both tofacitinib treatment groups in the background DMARD studies, similar differences from placebo in decreases in HAQ-DI were observed in patients discontinued from the prior TNF inhibitor treatment either due to lack of efficacy or intolerance. Results were consistent in the monotherapy studies; however, the numbers of patients were small.

8.10.6. Onset of Effect

ACR20

For both the background DMARD studies and the monotherapy studies, statistically significant differences from placebo in ACR20 response rates for both the 5 mg and 10 mg BID tofacitinib groups were seen as early as Week 2 (the first ACR assessment time point in the 6-month studies) or Month 1 (the first assessment time point in the 12-month studies) and maintained through the double blind treatment period (nominal $p < 0.05$) (Figure 8 and Figure 23).

ACR50 and ACR70

ACR50 and ACR70 responses were consistent with the ACR20 results in both background DMARD and monotherapy studies, with statistically significant differences from placebo seen as early as Week 2 or Month 1 for both tofacitinib dose groups. Nominal p-values for the comparisons with placebo were consistently <0.05 for all post baseline evaluation time points starting at Week 2 or Month 1 (Figure 8 and Figure 23).

HAQ-DI

HAQ-DI assessments showed that tofacitinib 5 mg and 10 mg BID treated patients exhibited significantly greater improvements in physical function compared to placebo as early as the time of first assessment (Week 2 or Month 1), and mean HAQ-DI improvements were maintained to Month 12 in tofacitinib-treated patients in both the background DMARD (Figure 12) and monotherapy studies.

8.10.7. Persistence of Efficacy

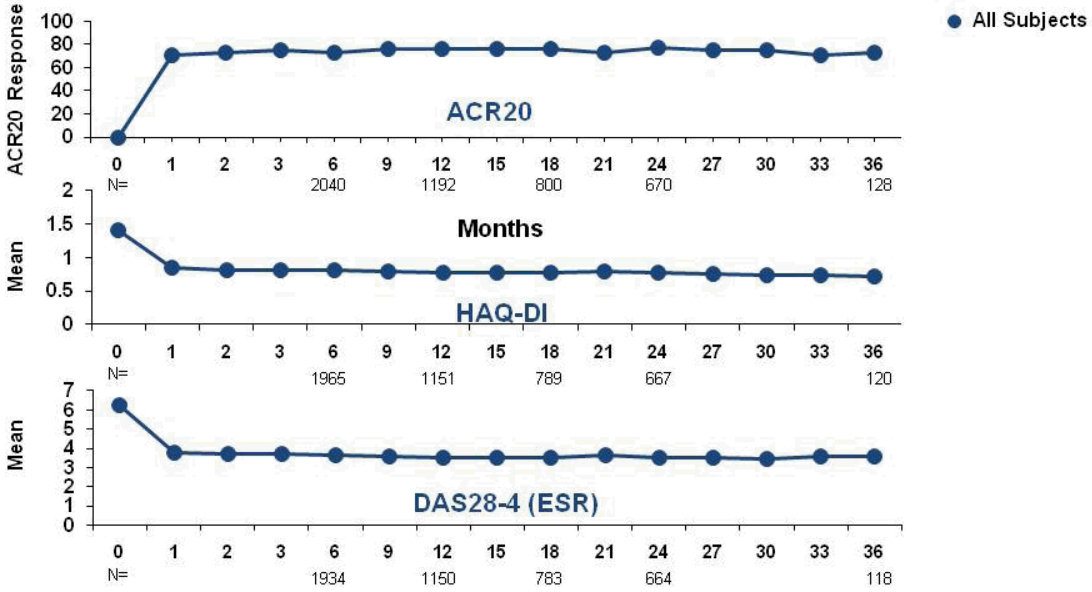
Persistence of efficacy for over 3 years has been demonstrated for both tofacitinib 5 mg and 10 mg treatment groups. Durability of effect was assessed in the three Phase 3 DMARD studies with duration of at least one year. Efficacy was maintained in all tofacitinib treatment

groups through the end of the 12 month period. Evidence of persistence of efficacy with tofacitinib treatment was also provided from data in the two ongoing, open-label, long term follow-up studies. Efficacy was maintained in these studies through 36 months.

Long-Term Extension Studies

Persistence of efficacy through 36 months of treatment with tofacitinib was observed in the open-label LTE studies A3921024 and A3921041. Durability of efficacy was assessed by ACR20, ACR50, ACR70 response rates, mean HAQ-DI, and mean DAS28-4(ESR) values that remain at or above levels considered to demonstrate continued responsiveness to tofacitinib treatment. These efficacy parameters were assessed in over 662 and 118 patients at 24 months and 36 months, respectively, in the LTE studies. Results for ACR20 response rates, HAQ-DI, and DAS28-4(ESR) are shown in Figure 29. ACR50 and ACR70 response results were similar to that for ACR20.

Figure 29. ACR20 Response Rates, HAQ-DI and DAS28-4(ESR) in Open Label Extension Studies (All Patients) – LTE Studies



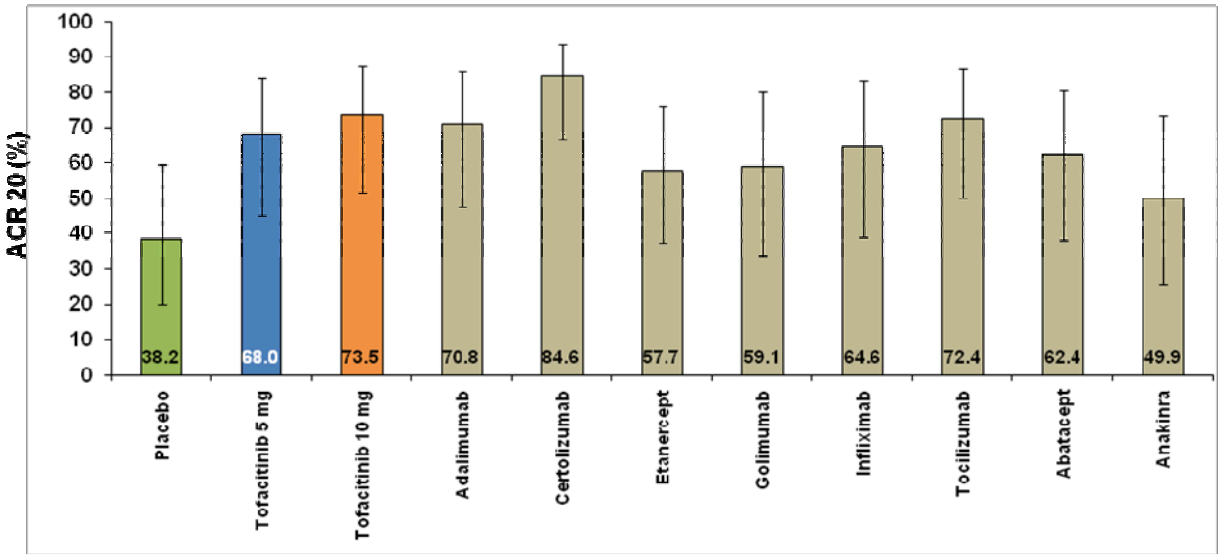
Note: the month "0" refers to the baseline of the qualifying randomized studies, the rest of the months were the months in the extension studies. LTE=long term extension

8.10.8. Mixed Treatment Comparison of the Efficacy of Tofacitinib versus Biologic DMARD Therapies

A mixed treatment comparison was performed to evaluate the efficacy of tofacitinib versus currently marketed biologic treatments for RA in patients who have had an inadequate response to nonbiologic DMARDs or TNF inhibitors. Treatment with tofacitinib 5 mg or 10 mg BID, alone or in combination with MTX, resulted in similar efficacy when compared

with the other interventions in almost all cases. The data on the outcomes of interest were extracted from the different studies and combined in meta-analysis models using fixed effects and random effects to estimate the relative efficacy of each of the competing interventions. Bayesian network-meta-analysis models were used to obtain the relative effect point estimates (difference in change from baseline (CFB) or odds ratios or rate ratios) and 95% credible intervals (95% CrI). Expected ACR20, 50, and 70 responses were based on the medians of the posterior distributions from the Bayesian analyses. Figure 30 presents the expected ACR20 responses for placebo, tofacitinib 5 and 10 mg BID, and marketed biologics on background MTX in patients who have had an inadequate response to MTX alone. Similar results were found for ACR50 and ACR70.

Figure 30. Expected ACR20 Response* at Month 3 from a Meta-Analysis of Randomized Clinical Trials of Tofacitinib and Multiple Biologic Agents in DMARD-IR Patients on Background MTX



* ACR20 responses are based on Bayesian network-meta-analysis models

8.11. Efficacy Conclusions

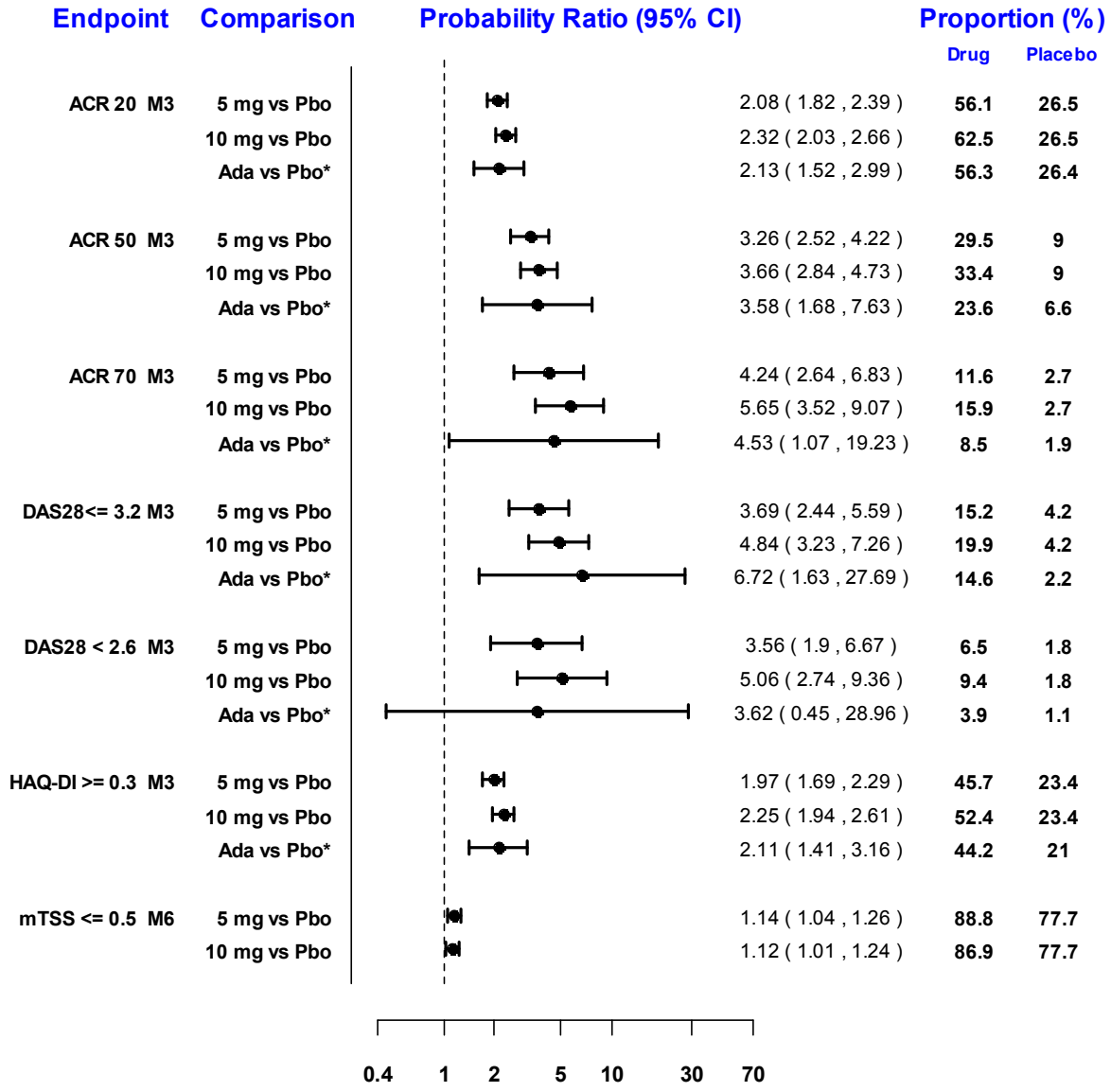
Results from five Phase 3 and four Phase 2 randomized, placebo controlled studies as well as data from 2 open-label, LTE studies, demonstrate that tofacitinib dosed either 5 mg or 10 mg BID was consistently efficacious whether given in combination with nonbiologic DMARDs or as monotherapy in the treatment of adult patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs.

Tofacitinib treatment provides consistent and robust improvements in measures of signs and symptoms, including ACR20 response and DAS28-4(ESR) <2.6. Tofacitinib slows the progression of structural damage as measured by changes from baseline in mTSS, and by the proportion of patients who did not have radiographic progression. Probability scores across pooled data are summarized in Figure 31 for primary and important secondary endpoints, all of which show robust and clinically meaningful improvement with tofacitinib. Treatment

with tofacitinib 5 mg or 10 mg BID were persistently efficacious in all efficacy assessments with the 10 mg BID dose being consistently more efficacious especially in more stringent measures such as ACR70 response rate and proportion of patients with DAS28-4(ESR) <2.6.

Consistent and robust improvements are also observed in patient-reported physical functioning, fatigue, and quality of life. The onset of efficacy is rapid, occurring within 2 weeks for some measures, and it is maintained for up to 3 years.

Figure 31. Probability Ratios for Proportion of Patients Achieving Selected Efficacy Endpoints, Tofacitinib versus Placebo (All Phase 3 Studies) and Adalimumab versus Placebo (1064/Standard Study)



Ada=Adalimumab; DAS28 = DAS28-4(ESR); M=Months; Pbo=Placebo
* Adalimumab versus placebo comparisons are based on study 1064/Standard; Non-responder imputation
Tofacitinib versus placebo comparisons are based on pooled estimates from 1032/Step, 1044/Scan, 1045/Solo, 1046/Sync, and 1064/Standard studies.

9. CLINICAL SAFETY

9.1. Presentation of Safety

This section provides a summary of the safety data for tofacitinib administered alone or in combination with MTX or other nonbiologic DMARDs for the treatment of RA. Patients participating in these studies had moderately to severely active RA with inadequate responses to treatment with at least one nonbiologic DMARD (typically MTX) and/or a biologic DMARD. Patients were treated with doses of tofacitinib 5 mg or 10 mg BID in the RA Phase 3 and LTE studies. For ease of discussion, 5 mg BID and 5 mg, as well as 10 mg BID and 10 mg, may be used interchangeably for treatment designation.

The population evaluated for safety included all patients who received at least 1 dose of study drug. Safety was assessed by collecting information on adverse events, deaths, serious adverse events, reasons for discontinuing from studies, laboratory tests and vital signs. AEs, SAEs, and discontinuations due to AEs are of treatment emergent events, unless otherwise noted. Subpopulation analyses of age, race, and gender were performed for the general safety parameters of AEs, SAEs, and discontinuations due to AEs. Results of these subgroup analyses are discussed herein only when a difference was noted.

Safety analyses include information submitted to the Agency in the clinical section of the NDA (data cut-off date of 29 March 2011) for general safety information. Additionally, information from the 4 month safety update (4MSU) report (data cut-off date of 29 September 2011) is used for deaths, serious infections, malignancies, and probable GI perforations. Updated SAEs and discontinuations due to AEs in the ongoing LTE studies are provided from the 4MSU report.

The two main safety populations discussed in this section include patients in the RA Phase 3 studies (pooled) and patients in the 2 LTE studies (pooled). The Phase 3 studies group includes data from the five Phase 3 RA studies which were pooled (1032/Step study, 1045/Solo study, 1046/Sync study, 1064/Standard study, and 1044/Scan study). Four of these studies were designed to administer tofacitinib along with a background DMARD (typically MTX), and one study administered tofacitinib as monotherapy. For the 2-year Phase 3 1044/Scan study, "completed" was defined as data up to the 12-month data collection point for participating patients. The Phase 3 studies were randomized, double-blind, placebo controlled studies and are presented to allow for comparison of tofacitinib to placebo over 3-6 months and, in one study, to the active control adalimumab over 12 months. Patients originally randomized to placebo were advanced to either tofacitinib 5 mg or 10 mg at 3 or 6 months, per protocol design, resulting in 3 treatment periods: 0 to 3 months (placebo-controlled portion of the studies), 3 to 6 months (some patients remain on placebo; some advance to tofacitinib treatment), and >6 months (no placebo group; all patients advance to tofacitinib treatment). In general, Phase 3 safety data are presented by the overall 0-12 months duration, except for adverse events, serious adverse events, and discontinuations due to adverse events where data are presented by treatment period as previously described.

The LTE group includes pooled data from the 2 ongoing LTE studies (1024/Sequel study and 1041 study) in which patients from Phase 2 or Phase 3 studies could continue participation

and receive tofacitinib 5 or 10 mg BID. Patients were allowed to continue on background RA therapy, including approved DMARDs and glucocorticoids. In the LTE studies, patients are followed over a longer period of time than in the Phase 3 studies, currently up to 3 years.

In addition, pooled safety data from RA Phase 2, Phase 3, and LTE studies (P2P3LTE pooling group) is presented for deaths, serious infections, including herpes zoster, malignancies, including lymphoma, and GI perforations. Duration of tofacitinib exposure in this pooled group was counted from first dose of tofacitinib to study completion or data cut-off.

It is important to note that as a result of the advancement of placebo patients to tofacitinib in the Phase 3 studies, the number of patients and duration of exposure to placebo is limited (681 patients and 203 PYO). Similarly, the exposure to the active control adalimumab was limited to one arm in a Phase 2 study (53 patients) and one arm in a Phase 3 study (204 patients and 178 PYO). Due to the limited amount of comparator data within the tofacitinib program, external comparator data was used to benchmark events of interest. A two-tier approach was used that considered clinical trial data as "tier 1" and observational data as "tier 2". Clinical trial data is the most relevant to the RA program population as patients come from the same baseline population from which patients in tofacitinib trials were sampled. Namely, persons eligible for trials for the treatment of moderate to severe RA. Data was gathered from a variety of such sources including: published clinical trials, regulatory submissions, and meeting abstracts. To enhance understanding of trends among persons with RA, observational data was also surveyed. The data sources included published data from disease and drug-specific registries, administrative claims databases and other national health care databases/surveys. To allow for a direct comparison to the tofacitinib safety database, data on rates versus proportions was extracted. Incidence rates provide a better representation of data as they consider censoring due to safety events and loss to follow-up. If rates were not published, the number of events and person-time accrued to calculate a rough estimate of risk in each study was used.

Note that in the LTE studies, patients in the tofacitinib 5 mg group had a longer exposure time (in total patient years of drug exposure) compared with the 10 mg group, therefore, direct comparison of percentages for AEs, SAEs, and discontinuations due to AEs between the 5 and 10 mg tofacitinib groups needs to be interpreted with caution as the percentages do not take into account the longer exposure time in the 5 mg group. Event rates, adjusted for patient years of observation, are provided for events of special interest, which take into account the time patients are exposed to drug.

9.2. Exposure

This safety summary includes safety data from 3030 patients who received tofacitinib in the Phase 3 studies, and data from 2 ongoing open-label, LTE studies of 3515 patients who were previously enrolled in double-blind Phase 2 or 3 studies, representing a total of nearly 7000 patient years of exposure to tofacitinib (Table 13).

Table 12, presents the numbers of patients in the RA Phase 2, Phase 3 and LTE studies in RA, in the treatment groups as originally randomized.

Table 12. Numbers of Patients in Rheumatoid Arthritis Studies, as Randomized and Treated

	Tofacitinib	Placebo	Adalimumab	Total
Phase 2 studies	1282	273	53	1608
Phase 3 studies	2430	681	204	3315
LTE studies	3515	--	--	3515*

Data as of 29 September 2011
LTE=long term extension studies.
* Patients in LTE studies were previously enrolled in a Phase 2 or 3 study and are not new patients.

Table 13, provides the numbers of patients and patient-years of exposure to any dose of tofacitinib in the Phase 2, Phase 3, LTE studies, and the P2P3LTE pooled group.

Table 13. Numbers of Patients and Patient-Years of Exposure in Rheumatoid Arthritis Studies, Patients Receiving Tofacitinib at Any Time

Study Phase	Numbers of Patients	Patient-Years of Exposure†
Phase 2 studies	1369	419.95
Phase 3 studies	3030	2210.97
LTE* studies	3515	4409.65
Phase 2 and 3 and LTE* studies	4791	6921.91

Data as of 29 September 2011
LTE=long-term extension studies.
* Patients in LTE studies were previously enrolled in a Phase 2 or 3 study and are not new patients
† Patient years of exposures in individual rows for Phase 2, Phase 3, and LTE do not match the number in the P2P3LTE row because the composite P2P3LTE figure does not contain patients from 2 blinded, ongoing studies who continued participation in the LTE studies.

Table 14 presents a summary of exposure for patients who received at least one dose of tofacitinib 5 mg or 10 mg for ≥6 months, ≥1 year, and ≥2 years.

Table 14. Clinical Trial Exposure to Tofacitinib 5 and 10 mg BID by Duration, in Completed Rheumatoid Arthritis Phase 2 and Phase 3 Studies and Long Term Extension Studies

	Tofacitinib			
Duration of exposure [a]	5 mg BID (N=1571)	10 mg BID (N=1761)	5 mg BID/ 10 mg BID[b] (N=1314)	5 and 10 mg BID[c] (N=4646)
≥6 months	1260	1494	1299	4053
≥1 year	1087	1120	1177	3384
≥2 years	601	125	263	989

Data as of 29 September 2011
a. Exposure to 5 or 10 mg BID only.
b. Patients in 5 mg/10 mg column represent those who received different doses between the index study and the extension study.
c. Patients in 5 mg BID, 10 mg BID, and 5 mg/10 mg columns are mutually exclusive, and their sum is represented in the 5 and 10 mg BID column, which summarizes distinct patients from Phase 2, Phase 3 and long -term extension studies.
In this table, the duration of 6 months is set to 175 days, 1 year is 350 days, and 2 years is 700 days, in accordance with the protocol windows.

9.3. Overview of Safety

Like other therapeutics that reduce the inflammation that underlies the disease in rheumatoid arthritis, tofacitinib has safety findings and potential risks in conjunction with its immunomodulatory mechanism. Tofacitinib is an immunomodulator with important safety findings and potential risks. These findings and potential risks include serious and other important infections, including tuberculosis and herpes zoster, malignancies including lymphoma, decreased neutrophil counts and neutropenia, and lipid elevations. The overall safety profile of tofacitinib, dosed at either 5 or 10 mg BID, is generally consistent with that observed in patients with moderately to severely active RA treated with biologic and nonbiologic DMARDs.

Tofacitinib therapy is also associated with changes in some laboratory values. Dose-dependent decreases in neutrophils and changes in hemoglobin were infrequently associated with adverse events such as neutropenia or anemia. Small increases in serum creatinine and increased creatine kinase were noted; these do not appear to represent significant safety risks for tofacitinib. Increases in lipids were noted, but do not appear to increase CV risk. Cases associated with hepatic transaminase elevations were carefully evaluated; the potential for hepatic toxicity appears to be low. Laboratory changes typically normalized upon discontinuation of tofacitinib treatment.

An overview of the number of patients with adverse events, SAEs, and discontinuations due to adverse events is presented below for the Phase 3 studies by study period (Table 15, Table 16, and Table 17) and the LTE studies (Table 18).

Table 15. Overview of Treatment Emergent Adverse Events (All Causality) in Phase 3 Studies (up to 3 Months): Number (%) of Patients

	Tofacitinib			Placebo	Adalimumab
	5 mg BID	10 mg BID	All Doses		
Patients evaluable for adverse events	1216	1214	2430	681	204
Number of adverse events	1321	1348	2669	690	182
Patients with adverse events	624 (51.3)	653 (53.8)	1277 (52.6)	363 (53.3)	105 (51.5)
Patients with serious adverse events	36 (3.0)	35 (2.9)	71 (2.9)	25 (3.7)	5 (2.5)
Patients with severe adverse events	49 (4.0)	39 (3.2)	88 (3.6)	28 (4.1)	6 (2.9)
Patients discontinued due to adverse events	52 (4.3)	49 (4.0)	101 (4.2)	22 (3.2)	10 (4.9)

Except for the total number of adverse events, patients are counted only once per treatment in each row.

Table 16. Overview of Treatment-Emergent Adverse Events (All Causality) in Tofacitinib All Doses and Placebo in All Phase 3 Studies (3 to 6 Months): Number (%) of Patients

	Tofacitinib			Placebo	Adalimumab
	5 mg BID	10 mg BID	All Doses		
Patients evaluable for adverse events	1451	1439	2890	221	204
Number of adverse events	1061	1067	2128	97	120
Patients with adverse events	579 (39.9)	556 (38.6)	1135 (39.3)	58 (26.2)	68 (33.3)
Patients with serious adverse events	47 (3.2)	37 (2.6)	84 (2.9)	7 (3.2)	6 (2.9)
Patients with severe adverse events	55 (3.8)	37 (2.6)	92 (3.2)	5 (2.3)	8 (3.9)
Patients discontinued due to adverse events	36 (2.5)	45 (3.1)	81 (2.8)	4 (1.8)	9 (4.4)

Except for the total number of adverse events, patients are counted only once per treatment in each row.

Table 17. Overview of Treatment-Emergent Adverse Events (All Causality) in Tofacitinib All Doses in All Phase 3 Studies (>6 Months): Number (%) of Patients

	Tofacitinib			Adalimumab
	5 mg BID	10 mg BID	All Doses	
Patients evaluable for adverse events	1056	1046	2102	204
Number of adverse events	883	1001	1884	142
Patients with adverse events	445 (42.1)	478 (45.7)	923 (43.9)	83 (40.7)
Patients with serious adverse events	34 (3.2)	32 (3.1)	66 (3.1)	7 (3.4)
Patients with severe adverse events	23 (2.2)	27 (2.6)	50 (2.4)	5 (2.5)
Patients discontinued due to adverse events	18 (1.7)	24 (2.3)	42 (2.0)	4 (2.0)

Data as of 29 March 2011
BID=twice daily
Except for the total number of adverse events, patients are counted only once per treatment in each row.

Table 18. Overview of Treatment-Emergent Adverse Events (All Causality) in All Long-Term Extension Studies (All Patients): Number (%) of Patients

	Tofacitinib		
	5 mg BID	10 mg BID	All Doses
Patients evaluable for adverse events	1321	1906	3227
Number of adverse events	4899	2848	7747
Patients with adverse events	1047 (79.3)	1088 (57.1)	2135 (66.2)

Table 18. Overview of Treatment-Emergent Adverse Events (All Causality) in All Long-Term Extension Studies (All Patients): Number (%) of Patients

	Tofacitinib		
	5 mg BID	**10 mg BID**	**All Doses**
Patients with serious adverse events	209 (15.8)	114 (6.0)	323 (10.0)
Patients with severe adverse events	153 (11.6)	98 (5.1)	251 (7.8)
Patients discontinued due to adverse events	148 (11.2)	75 (3.9)	223 (6.9)

Data as of 29 March 2011
BID=twice daily
Except for the total number of adverse events, patients are counted only once per treatment in each row.

9.4. Adverse Events

Adverse events experienced by tofacitinib patients were generally mild to moderate in severity and typically did not require permanent discontinuation. Overall, the adverse event profile observed with tofacitinib is generally consistent in terms of adverse event type and severity with safety profiles seen with TNF inhibitors and other biologic DMARDs.

Phase 3 Studies

The percentage of AEs was numerically similar between tofacitinib treatment groups and placebo during the placebo controlled period of the Phase 3 studies (Months 0-3) (Table 19). The most frequently reported AEs for tofacitinib treated patients were infections, with the respiratory tract being the most frequent site of infection. Differences in the frequency and severity of AEs between the tofacitinib 5 mg and 10 mg BID groups were small and variable; a dose response relationship was not noted for the incidence of AEs.

Overall, the AEs reported in the 3-6 month and > 6 month treatment periods of the Phase 3 studies were consistent with those reported in the 0-3 month treatment period (Appendix Table 67 and Table 68). Adverse events reported for patients in the Phase 3 background DMARD group and Phase 3 monotherapy group were similar, both in type of AE and frequency.

Table 19. Adverse Events by Decreasing Frequency* (All Causality, ≥ 2.0 % in Any Treatment Group) in Phase 3 (up to 3 Months): Number (%) of Patients

	Tofacitinib				
Preferred Term	**5 mg BID n=1216**	**10 mg BID n=1214**	**All Doses n=2430**	**Placebo n=681**	**ADA n=204**
Total patients with adverse events	***624 (51.3)***	***653 (53.8)***	***1277 (52.6)***	***363 (53.3)***	***105 (51.5)***
Upper respiratory tract infection	53 (4.4)	47 (3.9)	100 (4.1)	23 (3.4)	7 (3.4)
Headache	54 (4.4)	39 (3.2)	93 (3.8)	15 (2.2)	5 (2.5)
Nasopharyngitis	47 (3.9)	35 (2.9)	82 (3.4)	19 (2.8)	7 (3.4)
Diarrhoea	45 (3.7)	34 (2.8)	79 (3.3)	16 (2.3)	2 (1.0)
Nausea	32 (2.6)	25 (2.1)	57 (2.3)	18 (2.6)	3 (1.5)

Table 19. Adverse Events by Decreasing Frequency* (All Causality, ≥ 2.0 % in Any Treatment Group) in Phase 3 (up to 3 Months): Number (%) of Patients

	Tofacitinib				
Preferred Term	**5 mg BID n=1216**	**10 mg BID n=1214**	**All Doses n=2430**	**Placebo n=681**	**ADA n=204**
Total patients with adverse events	***624 (51.3)***	***653 (53.8)***	***1277 (52.6)***	***363 (53.3)***	***105 (51.5)***
Urinary tract infection	25 (2.1)	24 (2.0)	49 (2.0)	12 (1.8)	7 (3.4)
Hypertension	20 (1.6)	27 (2.2)	47 (1.9)	7 (1.0)	0
Dyspepsia	19 (1.6)	25 (2.1)	44 (1.8)	11 (1.6)	3 (1.5)
Oedema peripheral	17 (1.4)	21 (1.7)	38 (1.6)	16 (2.3)	3 (1.5)
Blood creatine phosphokinase increased	9 (0.7)	26 (2.1)	35 (1.4)	3 (0.4)	1 (0.5)
Bronchitis	14 (1.2)	13 (1.1)	27 (1.1)	10 (1.5)	4 (2.0)
Cough	11 (0.9)	16 (1.3)	27 (1.1)	11 (1.6)	4 (2.0)
Arthralgia	13 (1.1)	9 (0.7)	22 (0.9)	16 (2.3)	4 (2.0)
Rheumatoid arthritis	17 (1.4)	5 (0.4)	22 (0.9)	17 (2.5)	1 (0.5)
Rash	4 (0.3)	10 (0.8)	14 (0.6)	5 (0.7)	4 (2.0)

ADA=adalimumab; BID=twice daily.
*decreasing frequency by tofacitinib all doses group.
Note that the numbers and percentages of patients in the row for total patients with AEs and the SOC rows are based on the total numbers of AEs, rather than those meeting the 2% cutoff.
Except for the total number of adverse events, patients are counted only once per treatment in each row.

Long-Term Extension Studies

In the LTE studies, patients in the tofacitinib 5 mg group had a longer exposure time (in total patient years of drug exposure) compared with the 10 mg group (Table 20). Therefore, direct comparison of percentages between the 5 and 10 mg tofacitinib groups should be interpreted with caution as the percentages do not take into account the longer exposure time in the 5 mg group.

Similar to the Phase 3 studies, infection AEs were the most frequently reported. The most frequently reported AEs for patients receiving tofacitinib in the LTE studies are presented in (Table 21).

Table 20. Incidence Rates for Adverse Events (All Causality) in Long-Term Extension Studies

	Tofacitinib		
	5 mg BID	**10 mg BID**	**All Doses**
Total no. patients	1321	1906	3227
No. patients with AEs (%)	1047 (79.3)	1088 (57.1)	2135 (66.2)
Total patient-years of drug exposure	2236.4	881.9	3118.3
Exposure for event (pt-yr)	765.78	472.87	1238.66
Incidence rate, in events/100 pt-yr (95% CI)	136.723 (128.687, 145.261)	230.083 216.809, 244.169)	172.364 (165.206, 179.833)

Table 20. Incidence Rates for Adverse Events (All Causality) in Long-Term Extension Studies

	Tofacitinib		
	5 mg BID	**10 mg BID**	**All Doses**

BID=twice daily, pt-yr=patient-years.
Some events may have occurred after the end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.

Table 21 Adverse Events by Decreasing Frequency* (All Causality, ≥2% in Any Treatment Group) in Long Term Extension Studies: Number (%) of Patients

	Tofacitinib		
	5 mg BID	**10 mg BID**	**All Doses**
Preferred Term	**n=1321**	**n=1906**	**n=3227**
Total patients with adverse events	***1047 (79.3)***	***1088 (57.1)***	***2135 (66.2)***
Total pt-yr of drug exposure	***2236.4***	***881.9***	***3118.3***
Nasopharyngitis	230 (17.4)	92 (4.8)	322 (10.0)
Upper respiratory tract infection	101 (7.6)	135 (7.1)	236 (7.3)
Urinary tract infection	77 (5.8)	73 (3.8)	150 (4.6)
Bronchitis	92 (7.0)	54 (2.8)	146 (4.5)
Hypertension	92 (7.0)	45 (2.4)	137 (4.2)
Herpes zoster	90 (6.8)	43 (2.3)	133 (4.1)
Headache	79 (6.0)	40 (2.1)	119 (3.7)
Diarrhoea	68 (5.1)	42 (2.2)	110 (3.4)
Influenza	75 (5.7)	30 (1.6)	105 (3.3)
Back pain	76 (5.8)	31 (1.6)	107 (3.3)
Sinusitis	52 (3.9)	38 (2.0)	90 (2.8)
Rheumatoid arthritis	57 (4.3)	19 (1.0)	76 (2.4)
Cough	41 (3.1)	32(1.7)	73 (2.3)
Nausea	46 (3.5)	24 (1.3)	70 (2.2)
Fall	49 (3.7)	22 (1.2)	71 (2.2)
Arthralgia	41 (3.1)	26 (1.4)	67 (2.1)
Hypercholesterolaemia	45 (3.4)	20 (1.0)	65 (2.0)
Pharyngitis	45 (3.4)	17 (0.9)	62 (1.9)
Anaemia	36 (2.7)	21 (1.1)	57 (1.8)
Vomiting	36 (2.7)	22 (1.2)	58 (1.8)
Oedema peripheral	29 (2.2)	28 (1.5)	57 (1.8)
Contusion	38 (2.9)	21 (1.1)	59 (1.8)
Abdominal pain upper	37 (2.8)	18 (0.9)	55 (1.7)
Dyspepsia	35 (2.6)	21 (1.1)	56 (1.7)
Cystitis	42 (3.2)	12 (0.6)	54 (1.7)
Gastroenteritis	39 (3.0)	17 (0.9)	56 (1.7)
Alanine aminotransferase increased	37 (2.8)	17 (0.9)	54 (1.7)
Gastritis	31 (2.3)	20 (1.0)	51 (1.6)
Pyrexia	32 (2.4)	20 (1.0)	52 (1.6)
Rash	31 (2.3)	21 (1.1)	52 (1.6)

Table 21 Adverse Events by Decreasing Frequency* (All Causality, ≥2% in Any Treatment Group) in Long Term Extension Studies: Number (%) of Patients

	Tofacitinib		
	5 mg BID	**10 mg BID**	**All Doses**
Preferred Term	**n=1321**	**n=1906**	**n=3227**
Hyperlipidaemia	33 (2.5)	16 (0.8)	49 (1.5)
Blood creatine phosphokinase increased	27 (2.0)	19 (1.0)	46 (1.4)
Dizziness	30 (2.3)	15 (0.8)	45 (1.4)
Dental caries	33 (2.5)	9 (0.5)	42 (1.3)
Constipation	35 (2.6)	8 (0.4)	43 (1.3)
Osteoarthritis	26 (2.0)	16 (0.8)	42 (1.3)
Vertigo	31 (2.3)	8 (0.4)	39 (1.2)
Aspartate aminotransferase increased	30 (2.3)	10 (0.5)	40 (1.2)

BID=twice daily
* decreasing frequency by tofacitinib all doses group.
Except for the total number of adverse events, patients are counted only once per treatment in each row.

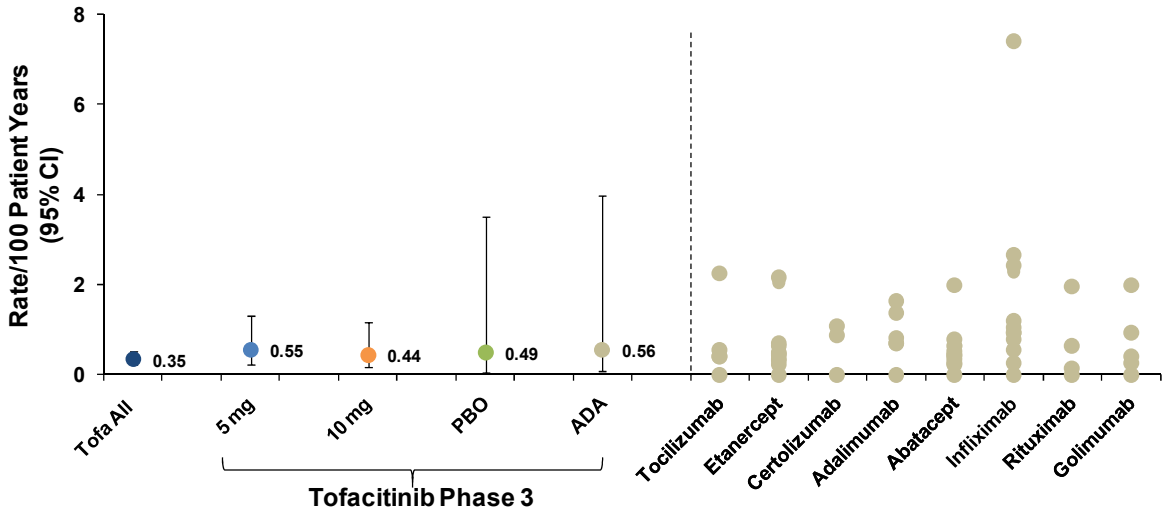
9.5. Serious Adverse Events

9.5.1. Deaths

The overall mortality rate of tofacitinib in the Phase 2, 3, and LTE studies was consistent with the adalimumab treatment group in Phase 3 and with published rates in RA clinical trials for TNF inhibitors and other biologic DMARDs (Gonzalez, 2007; Singer, 2003; Carmona, 2007) (Figure 32).

In the Phase 2, 3 and LTE studies for the RA development program, there were 44 deaths; 42 of these occurred in patients treated with tofacitinib, and 24 of those deaths occurred within 30 days of the patient discontinuing from study drug (Table 22., Table 23, and Table 24). The most common causes of death in the Phase 3 and LTE studies were infections and malignancies (Appendix Table 69 and Table 70).

Figure 32. Mortality Rates* for Tofacitinib, Placebo, and Adalimumab versus Clinical Trial Rates for TNF Inhibitors and Other Biologic DMARDs



CI=confidence interval; DMARD=disease modifying anti-rheumatic drug; Tofa All=mortality rate for all tofacitinib doses in pooled Phase 2, Phase 3, and long term extension studies
*Deaths occurring within 30 days of discontinuing drug are included in the graph
Bars for tofacitinib indicate 95% Confidence Limits.
Dots for comparator drugs represent point estimates of rates in randomized clinical trials from different published sources cited below. Darker dots indicate repeat values
References: Tocilizumab=tocilizumab data extracted from U.S. FDA Drug Approval Package, Actemra, 2010; Emery, 2008; Genovese, 2008-1; Jones, 2010; Etanercept=etanercept data extracted from Keystone, 2004; Weinblatt, 1999; Combe, 2006; van der Heijde, 2006; Klareskog, 2004; Bathon, 2000; Fernandez-Nebro, 2007; van Riel, 2006; Weinblatt, 2008; Emery, 2010-1;Certolizumab=certolizumab data extracted from Fleishmann, 2009; Smolen, 2009-2; Keystone, 2008; Adalimumab=adalimumab data extracted from Fernandez-Nebro, 2007; Chen, 2009; Furst, 2003; Weinblatt, 2006-1; Burmester, 2007; van de Putte, 2004; Miyasaka, 2008;Abatacept=abatacept data extracted from Weinblatt, 2007; Kremer, 2006; Kremer, 2008; Schiff, 2008; Westhovens, 2009-1; Weinblatt, 2006-2; Westhovens, 2009-2; Genovese, 2008-2; Infliximab=infliximab data extracted from Takeuchi, 2009; van Vollenhoven, 2009-1; St. Clair, 2004; Maini, 1999; Goekoop-Ruiterman, 2007; Fleischmann, 2005; Fernandez-Nebro, 2007; Maini, 2004; Schiff, 2008; Maini, 1998; van der Kooij, 2009; Pavelka, 2009; Abe, 2006; Rituximab=rituximab data extracted from Cohen, 2006; Emery, 2006; Emery, 2010-2; Rubbert-Roth, 2010; Golimumab=golimumab data extracted from U.S. FDA Drug Approval Package, Simponi, 2009; Kay, 2008; Smolen, 2009-1; Keystone, 2009; Emery, 2009; Keystone, 2010

Table 22. Incidence Rates for All-Cause Mortality (Death) Within 30 Days of Last Dose in Tofacitinib Treated Patients in Phase 2, Phase 3, and Long-Term Extension Studies

	Tofacitinib All Doses
Total no. patients	4791
No. (%) deaths	24 (0.5)
Exposure for event (pt-yr)	6921.89
Incidence rate, in events/100 pt-yr (95% CI)	0.347 (0.232, 0.517)

Data as of 29 September 2011
pt-yr=patient-years.
Cases from safety database.
Some events may have occurred after the end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.

9.5.1.1. Deaths in Phase 3 Studies

Overall, 14 deaths were reported during the Phase 3 RA studies: 7 in the tofacitinib 5 mg group, 5 in the tofacitinib 10 mg group, 1 in the placebo group, and 1 in the adalimumab group. Twelve deaths were reported within 30 days of discontinuation of study drug, 10 of which were patients receiving tofacitinib (Table 23). Two additional deaths were reported in the adalimumab group, between the 29 March 2011 cut-off date for the application and the 4MSU report cut-off date of 29 September 2011.

Table 23. Incidence Rates for All-Cause Mortality (Death) Within 30 Days of Last Dose in Phase 3 Studies (0 to 12 Months)

	Tofacitinib				
	5 mg BID	10 mg BID	All Doses	Placebo	Adalimumab
Total no. patients	1216	1214	3030	681	204
No. (%) deaths	5 (0.4)	4 (0.3)	10 (0.3)*	1 (0.1)	1 (0.5)
Exposure for event (pt-yr)	903.72	910.37	2098.19	202.55	178.94
Incidence rate, in events/100 pt-yr (95% CI)	0.553 (0.230, 1.329)	0.439 (0.165, 1.171)	0.477 (0.256, 0.886)	0.494 (0.070, 3.505)	0.559 (0.079, 3.967)

Data as of 29 March 2011
pt-yr=patient-years
* This number includes a patient who was initially assigned to placebo and was advanced to tofacitinib 10 mg treatment after receiving placebo for 3 months, per study design. This patient died after 47 days of treatment with tofacitinib 10 mg.
Cases from safety database; Some events may have occurred after the end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.

All deaths occurring within 30 days of last dose of study drug in the Phase 3 and the LTE studies after 25 February 2009 were adjudicated by the external, blinded Cardiovascular Safety Endpoint Adjudication Committee (CV SEAC) when supplemental data such as hospital records, death certificates, etc., were received by the committee. All deaths reported for the Phase 3 studies are presented in Appendix Table 69.

9.5.1.2. Deaths Long-Term Extension Studies

There were 28 deaths reported in the LTE studies as of 29 September 2011: 20 in the tofacitinib 5 mg group and 8 in the tofacitinib 10 mg group. Thirteen deaths were reported within 30 days of discontinuation of tofacitinib. All deaths reported for the LTE studies are presented in Appendix Table 70.

The incidence of deaths in the LTE studies was consistent with that in the Phase 3 index studies; the incidence rates for deaths for tofacitinib 5 and 10 mg in the LTE studies were similar to the rates with the same doses in the Phase 3 studies. The overall all-cause mortality rate within 30 days after the last dose of study treatment for patients receiving tofacitinib in the LTE studies was 0.295 deaths per 100 PYO (Table 24).

Table 24. Incidence Rates for All-Cause Mortality (Death) Within 30 Days of Last Dose in Long-Term Extension Studies

	Tofacitinib		
	5 mg BID	**10 mg BID**	**All Doses**
Total no. patients	1370	2145	3515
No. (%) deaths	10 (0.7)	3 (0.1)	13 (0.4)
Exposure for event (pt-yr)	2725.8	1683.8	4409.7
Incidence rate, in events/100 pt-yr	0.367	0.178	0.295
(95% CI)	(0.197, 0.682)	(0.057, 0.552)	(0.171, 0.508)

Data as of 29 September 2011
BID=twice daily, pt-yr=patient-years.
Cases from safety database.
Some events may have occurred after the end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.

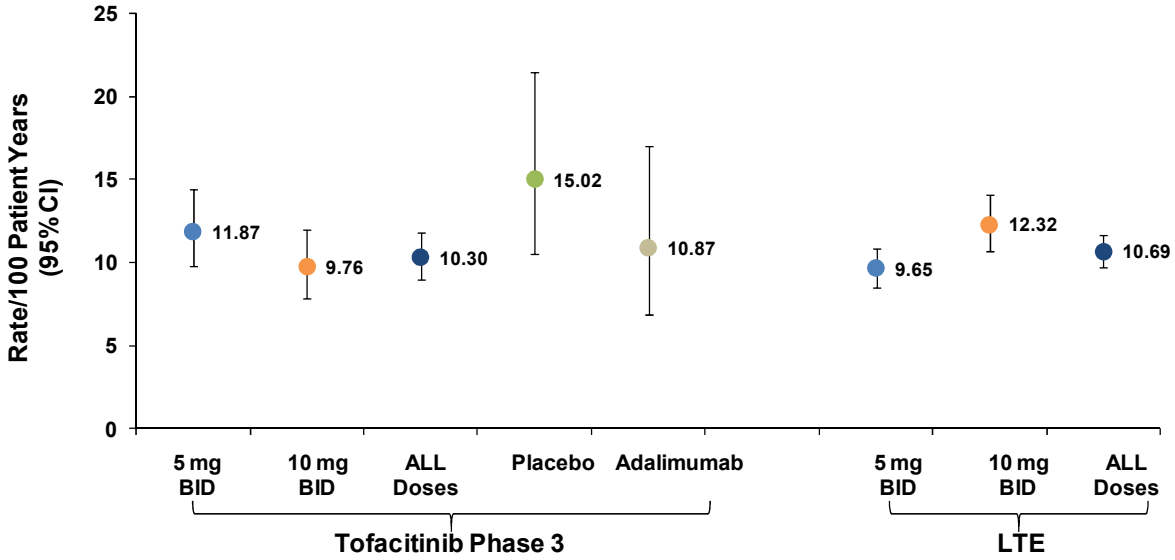
Phase 2 Studies

There were 2 deaths in Phase 2 studies, 1 of which occurred within 30 days of discontinuing tofacitinib treatment. One patient receiving tofacitinib 3 mg BID died of pneumonia, respiratory failure, and heart failure. A contributory role of tofacitinib to the event of pneumonia could not be ruled out. The other patient receiving tofacitinib 15 mg BID died of a cerebrovascular accident related to pre-existing hypertension; that death was not considered to be related to tofacitinib.

9.5.2. Other Serious Adverse Events

In the Phase 3 studies, the IRs of serious adverse events in the tofacitinib treatment groups were similar to the placebo and adalimumab treatment groups (Figure 33 and Table 25). Tofacitinib SAE rates in the LTE studies were consistent with the Phase 3 studies, demonstrating that SAE rates did not increase over time (Figure 33 and Table 26).

Figure 33. Serious Adverse Event Incidence Rates, by Treatment Group, Phase 3 and Long Term Extension Studies



5 mg BID=tofacitinib 5 mg twice daily; 10 mg BID=tofacitinib 10 mg twice daily; All doses=tofacitinib 5 and 10 mg BID doses; CI=confidence intervals; LTE=long term extension studies

Phase 3 Studies

The most frequently reported SAEs for tofacitinib treated patients were pneumonia (16), cellulitis (7), cholelithiasis (6), and herpes zoster (5) in the Phase 3 studies. The rates and types of SAEs when tofacitinib was dosed as monotherapy or with a background DMARD are similar to the overall Phase 3 SAE profile.

Tabular summaries of SAEs for Phase 3 studies are presented in Appendix III: 0-3 month period (Table 71), 3-6 month period (Table 72), and > 6 months period (Table 73).

Table 25. Incidence Rates for Serious Adverse Events in Phase 3 Studies (0 to 12 Months)

	Tofacitinib					
	5 mg BID	10 mg BID	5+10 mg BID	All Doses*	Placebo	Adalimumab
Total no. patients	1216	1214	2430	3030	681	204
No. (%) patients with events	104 (8.6)	87 (7.2)	191 (7.9)	211 (7.0)	30 (4.4)	19 (9.3)
Exposure for event (pt-yr)	872.61	890.43	1763.04	2044.36	199.68	174.82
Incidence rate, in events/100 pt-yr (95% CI)	11.867 (9.792, 14.381)	9.758 (7.909, 12.040)	10.803 (9.375, 12.449)	10.295 (8.995, 11.782)	15.024 (10.505, 21.488)	10.868 (6.932, 17.039)

Table 25. Incidence Rates for Serious Adverse Events in Phase 3 Studies (0 to 12 Months)

	Tofacitinib					
	5 mg BID	10 mg BID	5+10 mg BID	All Doses*	Placebo	Adalimumab

Data as of 29 March 2011
BID=twice daily, pt-yr=patient-years.
*The patients that are advanced from placebo to tofacitinib are counted in placebo until advancement and only in the tofacitinib All doses group after advancement.
Some events may have occurred after the end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.

Long-Term Extension Studies

In tofacitinib treated patients in the LTE studies, the most frequently reported SAEs included pneumonia (29), osteoarthritis (24), herpes zoster (10), fall (10), deep vein thrombosis (9), urinary tract infection (8), cholelithiasis (8), tendon rupture (8), femur fracture (8), cellulitis (7), and gastroenteritis (7) (Appendix Table 74).

SAEs in the LTE studies were reported for a greater percentage of patients in the tofacitnib 5 mg group (18.0%) than in the tofacitnib 10 mg group (9.3%), which is consistent with the longer exposure time for the tofacitinib 5 mg group compared with the tofacitinib 10 mg group. After controlling for the duration of exposure in the LTE studies, the incidence rate of SAEs in the tofacitnib 5 mg group is estimated to be 9.65 events per 100 PYO, compared with 12.32 events per 100 PYO for tofacitinib 10 mg (Table 26).

Table 26. Incidence Rates for All Serious Adverse Events in Long-Term Extension Studies

	Tofacitinib		
	5 mg BID	10 mg BID	All Doses
Total no. patients	1370	2145	3515
No. patients with SAEs (%)	246 (18.0)	200 (9.3)	446 (12.7)
Exposure for event (pt-yr)	2549.4	1622.9	4172.3
Incidence rate, in events/100 pt-yr	9.65	12.32	10.69
(95% CI)	(8.52, 10.93)	(10.73, 14.16)	(9.74, 11.73)

Data as of 29 September 2011
BID=twice daily, pt-yr=patient-years.
Some events may have occurred after the end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator

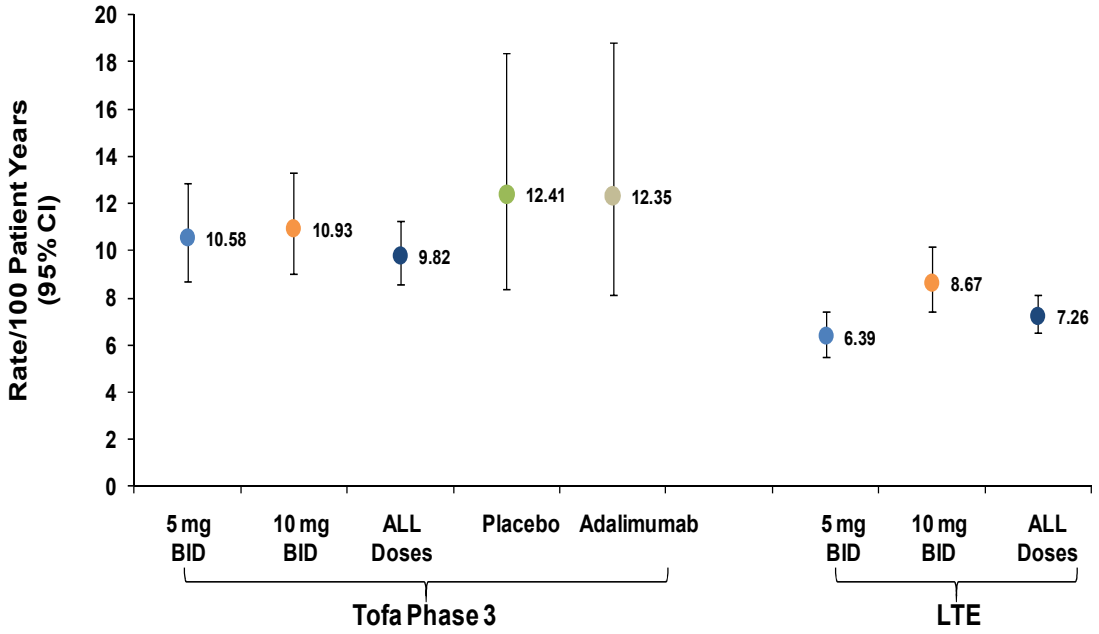
9.6. Discontinuations Due to Adverse Events

Phase 3 Studies

The rates of discontinuations due to adverse events in the Phase 3 studes were similar across the tofacitinib, placebo and adalimumab treatment groups (Figure 34). The most common AEs resulting in discontinuation in the tofacitinib group in the Phase 3 studies (0-12 months) were pneumonias (12; 0.4%), herpes zoster (11; 0.4%), and alanine aminotransferase (ALT) increased (9; 0.3%). The common in the placebo group was worsening rheumatoid arthritis

and the most common in the adalimumab treatment group was rash. AEs leading to discontinuation for Phase 3 are presented in Appendix Table 75 (0-3 months), Table 76 (3-6 months), and Table 77 (>6 months).

Figure 34. Discontinuations due to Adverse Events, by Treatment Group, Phase 3 and Long Term Extension Studies



5 mg BID=tofacitinib 5 mg twice daily; 10 mg BID=tofacitinib 10 mg twice daily; CI=confidence interval; LTE=long term extension studies; Tofa=tofacitinib

LTE Studies

The rate of discontinuations in the LTE studies was lower than in the Phase 3 studies, indicating that there was not an increase in rates over time (Figure 34). The percentage of patients discontinuing from the LTE studies due to an adverse event was numerically higher in the tofacitinib 5 mg group (12.6%) compared with the 10 mg group (6.8%), which is consistent with the longer duration of exposure for patients receiving tofacitinib 5 mg than for the 10 mg dose. The exposure-adjusted incidence rates for AEs leading to discontinuation from the LTE studies were 6.39 events and 8.67 events per 100 PYO for tofacitinib 5 mg and 10 mg groups, respectively.

The most common adverse events resulting in discontinuation from tofacitinib in the LTE studies were pneumonia (20; 0.6 %), herpes zoster (13; 0.4%), increased serum creatinine (12; 0.3%), and increased ALT (11; 0.3%). Appendix Table 78 presents AEs leading to discontinuation for the LTE studies.

9.7. Events of Special Interest

Determination of safety risks for patients treated with tofacitinib were based on the totality of the data including nonclinical observations, clinical observations, as well as safety risks associated with the general treated RA patient population.

Incidence rates are presented for events of special interest to put the event occurrence in context of the patient's time on treatment. In addition, incidence rates are compared to published data in patients with RA treated with TNF inhibitors and other biologic DMARDs, to provide context for the safety evaluation. As noted above, this comparison is particularly critical for important and less common safety events. Standardized incidence ratios are also presented for malignancies and lymphomas to facilitate comparison to rates of these events in the U.S. general population.

Analyses of subpopulations, including age and gender, were performed for the safety events of special interest, with other subgroups analyzed where clinically relevant or where indicated by results from subgroup analyses of general safety parameters (AEs, SAEs, discontinuations due to AEs). Glucocorticoid use was evaluated for serious infections; herpes zoster was further evaluated by patient race as an imbalance was observed in the AE subgroup analysis for race. Results of subgroup analyses are discussed herein only when a difference was noted.

9.7.1. Serious and Other Important Infections

Most infections occurring in patients receiving tofacitinib were mild to moderate, treatable, and did not require discontinuation of the drug. Fatal infections were uncommon and not related to the dose of tofacitinib. The rate, type, and temporal distribution of serious infections appear to be similar to that of other RA treatments, including TNF inhibitors and other biologic DMARDs (Curtis, 2007). The risk of infection in a patient is generally manageable with appropriate patient selection/screening, monitoring and antimicrobial therapy when warranted.

A serious infection was considered to be an infection that met the criteria of being a serious adverse event, specifically one that:

- Resulted in death;
- Was life-threatening (immediate risk of death);
- Required inpatient hospitalization or prolongation of existing hospitalization;
- Resulted in persistent or significant disability/incapacity; and/or
- Resulted in congenital anomaly/birth defect.

Infection events were the most common adverse events reported in clinical studies for tofacitinib. The most frequently reported serious infections with tofacitinib use included pneumonia, urinary tract infection, herpes zoster, cellulitis, gastroenteritis, diverticulitis, sepsis, and bronchitis. Opportunistic infections were uncommon and included tuberculosis and other mycobacterial infections, multidermatomal zoster, cryptococcus, candidiasis, pneumocystosis, cytomegalovirus (CMV) and BK virus.

Patients with RA are at a higher risk of infection than the general population. The risk of serious and opportunistic infections with tofacitinib is higher than was observed in the placebo and adalimumab treated patients, but similar to rates reported for biologic DMARDs. The overall incidence rate for herpes zoster was greater in patients receiving tofacitinib compared with published rates for RA patients receiving DMARD treatments (Section 9.7.1.3).

Patients ≥ 65 years of age appear to be at greater risk of any infection in the general RA population (Bathon, 2006; Galloway, 2011). Patients ≥65 years of age receiving tofacitinib were at increased risk of developing serious infections, herpes zoster, and opportunistic infections.

9.7.1.1. Serious Infections and Deaths Due to Infection

Serious Infections

A total of 206 patients reported a serious infection in the RA program (Phase 2, Phase 3, and LTE studies) as of 29 September 2011, yielding an incidence rate (IR) of 2.996 serious infections/100 PYO (Table 27).

Table 27. Incidence Rates for All Serious Infections in Phase 2, Phase 3 and Long Term Extension Studies (Tofacitinib Patients)

	All Tofacitinib Doses
Total no. patients	4791
No. (%) patients with events	206
Exposure for event (pt-yr)	6875.85
Incidence rate, in events per 100 pt-yr (95% CI)	2.996 (2.614, 3.434)

Data as of 29 September 2011
CI=confidence interval; pt-yr=patient years
Includes all AEs reported on the Infection log page that were marked as serious in the project database.
Some events may have occurred after the end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.

In Phase 3 studies, most infections were mild to moderate in severity and the percentage of patients experiencing severe infections was similar in all groups. Incidence rates for serious infections for Phase 3 studies are presented in Table 28; no clear difference in the rate between the 5 mg and 10 mg tofacitinib doses was observed.

Table 28. Incidence Rates for All Serious Infections in Phase 3 Studies, 0-12 months

	Tofacitinib			Placebo	Adalimumab
	5 mg BID	10 mg BID	All Doses		

Table 28. Incidence Rates for All Serious Infections in Phase 3 Studies, 0-12 months

	Tofacitinib			Placebo	Adalimumab
	5 mg BID	10 mg BID	All Doses		
Total no. patients	1216	1214	3030	681	204
No. (%) patients with events	29 (2.4)	27 (2.2)	61 (2.0)	3 (0.4)	3 (1.5)
Exposure for event (pt-yr)	900.87	909.08	2093.80	202.46	178.66
Incidence rate, in events per 100 pt-yr (95% CI)	3.217 (2.235, 4.629)	2.970 (2.037, 4.331)	2.912 (2.266, 3.743)	1.482 (0.478, 4.594)	1.679 (0.542, 5.206)

BID=twice a day; CI=confidence interval; pt-yr=patient years
Includes all AEs reported on the Infection log page that were marked as serious in the project database.
Some events may have occurred after the end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.

Overall, the data indicate that the 10 mg dose of tofacitinib is associated with a higher rate of infection (both serious and non serious) than the 5 mg dose, with this higher rate primarily observed during the LTE studies (Table 29).

Table 29. Incidence Rates for All Serious Infections in Long Term Extension Studies

	Tofacitinib		
	5 mg BID	10 mg BID	All Doses
Total no. patients	1370	2145	3515
No. (%) patients with events	63 (4.60)	68 (3.17)	131 (3.73)
Exposure for event (pt-yr)	2702.1	1675.7	4377.7
Incidence rate, in events per 100 pt-yr (95% CI)	2.332 (1.821, 2.985)	4.058 (3.200, 5.147)	2.992 (2.521, 3.551)

Data as of 29 September 2011
BID=twice a day; CI=confidence interval; pt-yr=patient years
Includes all AEs reported on the Infection log page that were marked as serious in the project database.
Some events may have occurred after the end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.

During long term treatment with tofacitinib, the rates of infections and serious infections appeared stable over time. Table 30 presents IRs for serious infections by 6-month intervals for the overall RA program.

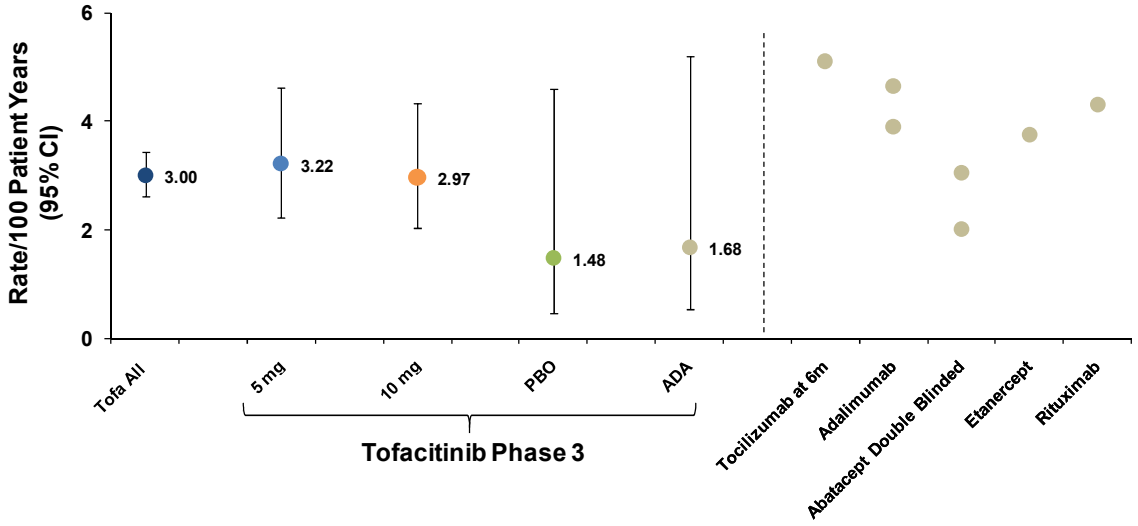
Table 30. Incidence Rates for All Serious Infections in Tofacitinib Treated Patients – by Six Month Intervals in Phase 2, 3, and LTE Studies

	Overall	0-6 Months	6-12 Months	12-18 Months	18-24 Months	>24 Months
Total Pts. Exposure (n)	4791	4791	4003	3106	2037	930
Total Pt-yr of Drug Exposure	6921.9	2166.5	1808.1	1223.4	731.1	963.6
Serious Infection Events						
Unique Pts with events (n)	206	60	65	41	23	17
Incidence (proportion)	0.0430	0.0125	0.0162	0.0132	0.0113	0.0183
Total Pt-yr of Exposure for Event	6875.9	2163.4	1804.0	1219.8	730.0	958.7
Incidence Rate per 100 pt-yr (95% CI) - Crude	3.00 (2.61, 3.43)	2.77 (2.15, 3.57)	3.60 (2.83, 4.60)	3.36 (2.48, 4.57)	3.15 (2.09, 4.74)	1.77 (1.10, 2.85)

CI=confidence interval; LTE=long term extension; pt-yr=patient years

The risk of serious and opportunistic infections with tofacitinib is higher than was observed in the placebo and adalimumab treated patients, but similar to rates reported for biologic DMARDs (Figure 35).

Figure 35. Serious Infections Incidence Rates (95% CI) for Tofacitinib versus Clinical Trial Data for TNF Inhibitors and Other Biologic DMARDs



Bars indicate 95% Confidence Limits.
Dots for other drugs represent point estimates found in different published sources.
DMARDs=disease modifying antirheumatic drugs; OL=open label studies; PYO=patient years of observation; TNF=tumor necrosis factor; TNFi=tumor necrosis factor inhibitors; Tofa All=tofacitinib 5 mg and 10 mg BID doses; Tofa Phase 3=treatment groups from the Phase 3 studies:5 mg=tofacitinib 5 mg BID, 10 mg=tofacitinib 10 mg BID, PBO=placebo,ADA=adalimumab;DB=double blind studies; 6m=6 months.
Tofa All data as of 31 September 2011. Tofacitinib Phase 3 data as of 29 March 2011
References: Tocilizumab 6m=tocilizumab 6 month data extracted from U.S. FDA Drug Approval Package, Actemra, 2010; Adalimumab=adalimumab data extracted from Abbott Laboratories, Humira, 2011; U.S. FDA, Drug Approval Package, Humira, 2008; Abatacept DB=abatacept double blind data extracted from Schiff , 2010; Lacaille, 2009; Abatacept

DB=abatacept double blind data extracted from Schiff , 2010; Lacaille, 2009; Etanercept=etanercept data extracted from Gottlieb, 2011;Rituximab= rituximab data extracted from U.S. FDA, Label, Rituxan, 2011.

Deaths due to Infections

Out of the 42 deaths in patients receiving tofacitinib in the RA program as of 29 September 2011, infection was the cause of death in 9 tofacitinib treated patients: 6 deaths in the 5 mg BID group, 2 deaths in the 10 mg BID group, and 1 death in the 3 mg BID group (Phase 2).

9.7.1.2. Subpopulations for Serious and Other Important Infections

Incidence rates of serious infections by age, gender, and glucocorticoid use in the Phase 3 and LTE studies are presented in Table 31 andTable 32. Patients ≥65 years of age receiving tofacitinib were at increased risk of developing serious infections. The age-related increase in the serious infection rate was more apparent with the 10 mg dose of tofacitinib compared with the 5 mg dose in the LTE studies, in contrast to the Phase 3 studies where patients ≥65 years of age had a greater incidence of serious infections in the 5 mg group. Increased rates for these events in patients ≥65 years of age is consistent with published clinical trial and observational reports in patients with RA treated with nonbiologic DMARDs and TNF inhibitors (nonbiologic DMARD IR range: 1.4-4.1 events/100 PYO; TNF inhibitor IR range: 2.6-18.1 events/100 PYO) (Abbott Laboratories, Humira, 2011; Curtis, 2007; Wolfe, 2007; Strangfeld, 2009; Bathon, 2006; Galloway, 2011; Evans, 2011; U.S. FDA, Drug Approval Package, Humira, 2008). Male gender and glucocorticoid use also appeared to increase the risk of serious infections, but the effect was not as large as that of age.

Table 31. Incidence Rate of Serious Infections According to Demographic Characteristics and Glucocorticoid Use, All Phase 3 Studies (0 to 12 Months)

		Incidence Rate per 100 Patient-years (95% CI)			
		Tofacitinib 5 mg BID	**Tofacitinib 10 mg BID**	**Placebo**	**Adalimumab**
Age	<65	2.466 (1.573, 3.866)	2.686 (1.751, 4.120)	1.728 (0.557, 5.358)	0.653 (0.092, 4.632)
	≥65	7.626 (4.103, 14.173)	4.712 (2.117, 10.488)	0	7.870 (1.968, 31.468)
Gender	Male	4.992 (2.380, 10.471)	5.669 (2.835, 11.335)	0	0
	Female	2.890 (1.903, 4.389)	2.474 (1.578, 3.879)	1.810 (0.584, 5.613)	2.128 (0.686, 6.599)
Glucocorticoids	Yes	4.959 (3.351, 7.339)	2.751 (1.629, 4.645)	2.649 (0.854, 8.215)	1.958 (0.490, 7.831)
	No	1.006 (0.378, 2.682)	3.249 (1.886, 5.595)	0	1.307 (0.184, 9.275)

BID = twice a day; CI = Confidence interval

Table 32. Incidence Rate of Serious Infections According to Demographic Characteristics and Glucocorticoid Use, Long Term Extension Studies

		Incidence Rate per 100 Patient-years (95% CI)		
		Tofacitinib 5 mg BID	**Tofacitinib 10 mg BID**	**All Tofacitinib**
Age	<65	2.080 (1.563, 2.768)	2.983 (2.204, 4.036)	2.426 (1.971, 2.987)
	≥65	3.619 (2.217, 5.907)	9.720 (6.618, 14.276)	5.919 (4.374, 8.009)
Gender	Male	2.367 (1.311, 4.274)	6.398 (4.031, 10.156)	3.887 (2.701, 5.593)
	Female	2.324 (1.771, 3.050)	3.586 (2.718, 4.731)	2.809 (2.313, 3.410)
Glucocorticoids	Yes	2.587 (1.819, 3.678)	5.855 (4.015, 8.538)	3.495 (2.702, 4.521)
	No	1.856 (1.184, 2.910)	3.830 (2.346, 6.251)	2.428 (1.744, 3.382)

Data for age and gender as of 29 September 2011; Data for glucocorticoids as of 29 March 2011
BID=twice a day; CI=confidence interval.

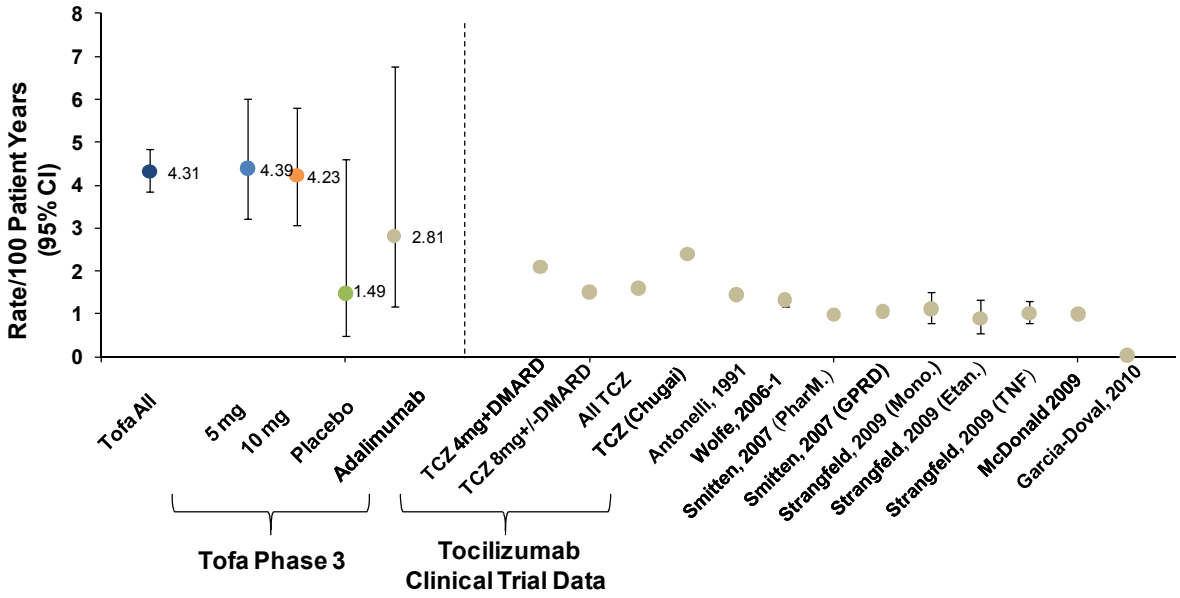
9.7.1.3. Herpes Zoster

Herpes zoster is a common skin disorder caused by the reactivation of latent varicella-zoster virus. Herpes zoster risk is increased in conditions with depressed cell-mediated immunity, including malignancy, HIV, transplantation, autoimmune disorders and immunosuppressive / immunomodulatory therapies. The risk of herpes zoster appears increased in patients with RA compared with the general population (Smitten, 2007; Strangfeld, 2009; Wolfe, 2006).

The majority of herpes zoster events were mild or moderate in severity and infrequently met seriousness criteria or resulted in permanent discontinuation. In all treatment groups, herpes zoster rates were higher among DMARD recipients; the incidence rate of herpes zoster did not appear to increase after long-term treatment.

Rates of herpes zoster infections in tofacitinib and adalimumab treated patients with RA were increased compared with placebo treated patients and observational published rates for RA patients receiving DMARD treatments (Figure 36). Sources for observational data include RA registries, claims data, health records, biologic DMARD database from countries including the US, Germany, Spain, and UK. Unless otherwise noted, incidence rates presented include both non-serious and serious herpes zoster events; the large majority were non-serious.

Figure 36. Herpes Zoster Rates in Tofacitinib, Placebo, Adalimumab versus Clincal Trial and Observational Data for TNF Inhibitors and Other Biologic DMARDs



CI=confidence interval; DMARD=disease modifying anti-rheumatic drug; TNF=tumor necrosis factor;Tofa All=tofacitinib data from Phase 2, Phase 3, and LTE studies; Tofa Phase 3=tofacitinib data from Phase 3 studies: 5 mg=tofacitinib 5 mg BID; 10 mg=tofacitinib 10 mg BID;
Comparator data: US FDA Tocilizumab Advisory Committee Mtg, 2008; US FDA Tocilizumab Drug Approval Package, 2010.Antonelli, 1991; Wolfe, 2006; Smitten, 2007; Strangfeld, 2009; McDonald, 2009; Garcia-Doval, 2010.

The overall IR rate of herpes zoster in tofacitinib treated patients in the RA program is 4.315 events/100 PYO (Table 33).

Table 33. Incidence Rates for All Herpes Zoster, Phases 2 and 3 and LongTerm Extension Studies

	All Tofacitinib
Total no. patients	4791
No. (%) patients with events	288 (6.0)
Exposure for event (pt-yr)	6674.00
Incidence rate, in events per 100 pt-yr (95% CI)	4.315 (3.845, 4.844)

CI=confidence interval; pt-yr=patient year

During the Phase 3 studies, the exposure adjusted IRs for herpes zoster were higher among tofacitinib recipients compared with patients in placebo or adalimumab groups (Table 34). The IRs for all herpes zoster infections in tofactinib treated patients did not appear to increase with long term follow-up in the LTE studies and remained similar between tofacitinib recipients regardless of dose (Table 35). In addition, when analyzing later periods of follow-up (>12 months) in the combined Phase 2, 3, and LTE studies, the IR for all herpes zoster infections did not increase over time (Table 36).

Table 34. Incidence Rates for All Herpes Zoster Virus Infections in Phase 3 Studies, (0-12 months)

	Tofacitinib			Placebo	Adalimumab
	5 mg BID	10 mg BID	All		
Total no. patients	1216	1214	3030	681	204
No. (%) patients with events	39 (3.2)	38 (3.1)	90 (3.0)	3 (0.4)	5 (2.5)
Exposure for event (pt-yr)	885.66	895.25	2060.30	201.68	177.72
Incidence rate, in events per 100 pt-yr (95% CI)	4.391 (3.208, 6.009)	4.231 (3.079, 5.815)	4.355 (3.542, 5.354)	1.487 (0.480, 4.612)	2.813 (1.171, 6.759)

Data as of 29 March 2011
BID=twice a day; CI=confidence interval; pt-yr=patient-years
Some events may have occurred after the end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.

Table 35. Incidence Rates for All Herpes Zoster Virus Infections in Long-Term Extension Studies

	Tofacitinib		
	5 mg BID	10 mg BID	All
Total no. patients	1370	2145	3515
No. (%) patients with events	106 (7.74)	78 (3.64)	184 (5.23)
Exposure for event (pt-yr)	2592.35	1646.92	4239.27
Incidence rate, in events per 100 pt-yr (95% CI)	4.089 (3.380, 4.946)	4.736 (3.794, 5.913)	4.340 (3.756, 5.015)

Data as of 29 September 2011
BID=twice a day; CI=confidence interval; pt-yr=patient-years
Some events may have occurred after the end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.

Table 36. Incidence Rates for All Herpes Zoster, by 6 Month Intervals, in Phases 2 and 3 and LongTerm Extension Studies

	0-6 Months	6-12 Months	12-18 Months	18-24 Months	> 24 Months
Total no. patients	4791	3945	3011	1951	881
No. (%) patients with events	94 (2.0)	87 (2.2)	50 (1.7)	27 (1.4)	30 (3.4)
Exposure for event (pt-yr)	2149.72	1761.51	1174.88	692.45	895.44
Incidence rate, in events per 100 pt-yr (95% CI)	4.373 (3.572, 5.352)	4.939 (4.003, 6.094)	4.256 (3.226, 5.615)	3.899 (2.674, 5.686)	3.350 (2.342, 4.792)

CI=confidence interval

Serious Herpes Zoster Cases

Five patients in the Phase 3 studies and 11 patients in the LTE studies reported a serious herpes zoster infection. No cases of serious herpes zoster occurred among patients who received tofacitinib monotherapy, or those who received placebo or adalimumab. Incidence rates of serious cases of herpes zoster were similar in the Phase 3 and LTE studies (Table 37). One case of multidermatomal herpes zoster was observed in a patient in the tofacitinib 5 mg group in a Phase 3 study. There were no cases of visceral or central nervous system dissemination of zoster.

Table 37. Incidence Rates for Serious Herpes Zoster Virus Infections in Phase 3 and Long Term Extension Studies

	Tofacitinib		
	5 mg BID	**10 mg BID**	**All**
Phase 3 Studies			
Total no. patients	1216	1214	3030
No. (%) patients with events	4 (0.3)	1 (<0.1)	5 (0.2)
Exposure for event (pt-yr)	903.63	910.37	2098.10
Incidence rate, in events per 100 pt-yr (95% CI)	0.443 (0.166, 1.179)	0.110 (0.015, 0.780)	0.238 (0.099, 0.573)
Long Term Extension Studies			
Total no. patients	1370	2145	3515
No. (%) patients with events	9 (0.66)	2 (0.09)	11 (0.31)
Exposure for event (pt-yr)	2723.23	1683.36	4406.59
Incidence rate, in events per 100 pt-yr (95% CI)	0.330 (0.172, 0.635)	0.119 (0.030, 0.475)	0.250 (0.138, 0.451)

Phase 3 data as of 29 March 2011; LTE data as of 29 September 2011
BID=twice a day; CI=confidence interval; pt-yr=patient-years
Some events may have occurred after the end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.

9.7.1.3.1. Herpes Zoster in Subpopulations

A multivariate analysis was performed to assess the potential association of herpes zoster with several possible predictors in patients treated with tofacitinib. The potential predictors

considered included age, gender, gender, self-reported race, tropical geographic location, weight, body mass index, smoking history; baseline, changes from baseline, and extrema of neutrophils, lymphocytes, DAS, LDL-c; and also concomitant DMARD use, concomitant glucocorticoid use, and tofacitinib dose. The only factors indicated as potentially associated with herpes zoster in this multivariate analysis were limited to Asian race (increased, strongly associated) and duration of RA disease (longer duration of RA disease was associated with increased risk, weakly associated).

Asian patients had a higher rate of herpes zoster than other races both when treated with tofacitinib or placebo (Table 38).

Table 38. Incidence Rates for All Herpes Zoster by Race, in Phases 2, 3 and LongTerm Extension Studies, Tofacitinib Patients

	White	Black	Asian	Other
Total no. patients	2876	139	1327	443
No. (%) patients with events	140 (4.9)	4 (2.9)	126 (9.5)	17 (3.8)
Exposure for event (pt-yr)	4165.1	161.9	1749.9	589.1
Incidence rate, in events per 100 pt-yr (95% CI)	3.361 (2.848, 3.967)	2.471 (0.927, 6.583)	7.201 (6.047, 8.574)	2.886 (1.794, 4.642)

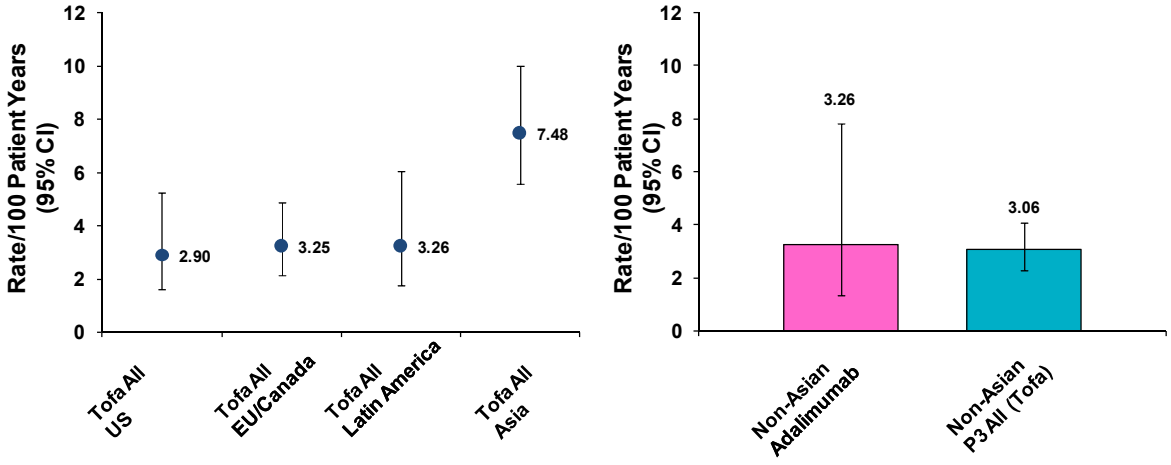
CI=confidence interval; pt-yr=patient-years.

The 1064/Standard study, in which adalimumab was used as an active comparator, was primarily conducted in the US and Europe and the percent of Asian patients in the adalimumab treatment group was less than in the tofacitinib treatment groups. The higher rate of herpes zoster in the RA program, and particularly in the tofacitinib-treated patients, may be partially explained by the higher rate observed in patients of Asian race, which comprised approximately 25% of patients studied in the Phase 3 trials.

An evaluation of the impact of geographic region and race on rates of herpes zoster was conducted. Figure 37 shows the higher rate of herpes zoster in tofacitinib treated patients in Asia compared to other regions. In contrast, non-Asian patients treated with tofacitinib in the Phase 3 studies and non-Asian patients treated with adalimumab in the Phase 3 1064/Standard study had similar herpes zoster rates (Figure 37). None of the 19 Asian patients not living in Asian countries reported herpes zoster.

The rate of herpes zoster in tofacitinib treated patients will be further studied in post-marketing studies.

Figure 37. Rate of Herpes Zoster by Geographic Region and in Non-Asian Race Treatment Groups



Non-Asian Adalimumab=Non-Asian patients in the adalimumab group; Non-Asian P3All (Tofa)l=Non-Asian tofacitinib patients in the Phase 3 studies; Tofa All US= all tofacitinib patients from study sites in the United States; Tofa All EU/Canada= all tofacitinib patients from study sites in the European Union and Canada; Tofa All Latin America= all tofacitinib patients from study sites in Latin America; Tofa All Asia: all tofacitinib patients from study sites in Asia

It should be noted that recent presentations and publications have shown an increase in the rate of herpes zoster in the RA population. It is not clear whether this represents an actual increase in incidence or an increase in awareness in the RA community (Veetil, 2011).

9.7.1.4. Tuberculosis and Other Opportunistic Infections

9.7.1.4.1. Tuberculosis

Patients in the Phase 2 and 3 studies were screened for latent and active tuberculosis (TB) infections with a chest x-ray and either an interferon-gamma release assay (QuantiFERON-TB Gold In-Tube test) or a purified protein derivative tuberculin skin test before randomization. Patients with latent TB infection were allowed to enroll in the Phase 3 studies after receiving approximately 1 month of isoniazid therapy, provided they still met the inclusion/exclusion criteria. Patients with latent TB in the Phase 3 studies were required to complete a 9-month course of isoniazid. There was no requirement for rescreening before entry into the LTE studies nor for periodic rescreening during participation in the LTE studies.

The most common opportunistic infection in the RA population was TB. There were 12 cases of TB in the RA program, 11 of which occurred in countries with high overall rates of TB, including China, India, Korea, Mexico, the Philippines and Thailand (WHO TB burden estimates). One of the 12 cases occurred in the United States 2 months after the patient discontinued from the 1024/Sequel LTE study. This case was entered into the safety database, but was not entered into the study database. This case was therefore not included in the incidence rate calculations cited in Table 39, below.

The incidence rates for tuberculosis in the Phase 3 and LTE studies are presented in Table 39. Of the 12 TB cases in the tofacitinib program, 9 occurred in the tofacitinib 10 mg group and 3 occurred in the tofacitinib 5 mg group. Eight of the TB cases were confined to the lung and 4 involved extra-pulmonary dissemination. No cases of TB occurred in patients who had latent TB at study enrollment. No cases of TB were reported among placebo or adalimumab recipients.

These results suggest that TB may be more frequent among patients receiving tofacitinib 10 mg than 5 mg. The TB rates in patients treated with tofacitinib living in areas with a higher prevalence of TB infection are consistent with the rates observed in RA patients treated with TNF inhibitors in those areas. An association has been noted between RA and TB with the risk elevated in RA patients compared to the general population (Keane, 2001; Carmona, 2003; Wolfe, 2004; Askling, 2005; Yamada, 2006; Seong, 2007).

Table 39. Incidence Rates for Tuberculosis in Phase 3 and Long Term Extension Studies

	Tofacitinib		
	5 mg BID	**10 mg BID**	**All Doses**
Phase 3 Studies			
Total no. patients	1216	1214	3030
No. (%) patients with events	0	6 (0.5)	6 (0.2)
Exposure for event (pt-yr)	903.72	910.17	2097.99
Incidence rate, in events per 100 pt-yr (95% CI)	0	0.659 (0.296, 1.467)	0.286 (0.128, 0.637)
Long Term Extension Studies			
Total no. patients	1370	2145	3515
No. (%) patients with events	2 (0.15)	3(0.14)	5(0.14)
Exposure for event (pt-yr)	2725.70	1683.66	4409.36
Incidence rate, in events per 100 pt-yr (95% CI)	0.073 (0.018, 0.293)	0.178 (0.057, 0.552)	0.113 (0.047, 0.272)

Phase 3 data as of 29 March 2011
LTE studies data as of 29 September 2011
BID=twice a day; CI=confidence interval;LTE=long term extension pt-yr=patient-years.
Some events may have occurred after end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.

9.7.1.4.1.1. Tuberculosis in Subpopulations

Incidence rates for tuberculosis by age, gender, and glucocorticoid use are presented for Phase 3 studies (Table 40) and LTE studies (Table 41).

Age appears to be a factor associated with the development of TB in the LTE studies: the incidence rate among patients ≥65 years of age was numerically higher compared with patients <65 years of age. Male gender appeared to be the only factor associated with the development of TB in the Phase 3 studies; in the LTE studies, both TB cases occurred among women. Glucocorticoid use did not appear to associated with incidence of TB infections in the Phase 3 or LTE studies.

Table 40. Incidence Rate of Tuberculosis According to Demographic Characteristics and Glucocorticoid Use in All Phase 3 Studies (0-12 Months)

		Incidence Rate per 100 Patient-years (95% CI)			
		Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo	Adalimumab
Age	<65	0	0.639 (0.266, 1.535)	0	0
	≥65	0	0.783 (0.110, 5.555)	0	0
Gender	Male	0	2.120 (0.684, 6.574)	0	0
	Female	0	0.390 (0.126, 1.210)	0	0
Glucocorticoids	Yes	0	0.589 (0.190, 1.826)	0	0
	No	0	0.749 (0.241, 2.321)	0	0

Data as of 29 March 2011
BID=twice a day; CI=confidence interval

Table 41. Incidence Rate of Tuberculosis According to Demographic Characteristics in Long Term Extension Studies

		Incidence Rate per 100 Patient-years (95% CI)		
		Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	All
Age	<65	0.088 (0.022, 0.351)	0.071 (0.010, 0.502)	0.081 (0.026, 0.252)
	≥65	0	0.740 (0.185, 2.958)	0.278 (0.070, 1.113)
Gender	Male	0	0	0
	Female	0.089 (0.022, 0.354)	0.214 (0.069, 0.664)	0.137 (0.057, 0.328)
Glucocorticoids	Yes	0	0	0
	No	0.097 (0.014, 0.688)	0.238 (0.034, 1.692)	0.138 (0.034, 0.551)

Data for age and gender as of 29 September 2011; Data for glucocorticoids as of 29 March 2011
BID=twice a day; CI=confidence interval.

9.7.1.4.2. Other Opportunistic Infections

There were 33 patients with opportunistic infections observed in the RA Phase 3 studies (14) and LTE studies (19). No opportunistic infections were observed in the placebo or adalimumab groups. The opportunistic infection incidence rate in the Phase 3 studies was higher in tofacitinib 10 mg treated patients (1.099 events/100 PYO) compared with tofactinib 5 mg treated patients (0.332 events/100 PYO), but the incidence rates were similar in the

LTE studies (tofacitinib 5 mg=0.368 events/100 PYO, tofacitinib 10 mg=0.535 events/100 PYO; overall tofacitinib=0.432 events/PYO).

In the tofacitinib RA development program, opportunistic infections were uncommon, and, in addition to the tuberculosis cases discussed above, included cases of esophageal candidiasis (7), pneumocystis jirovecii pneumonia (3), CMV viremia/infections (4), non-tuberculosis mycobacterial lung infections (2), cryptococcal pneumonia (2), and one case each of multidermatomal herpes zoster infection, BK encephalopathy, and cryptococcal meningitis. The rate of opportunistic infections observed in the Phase 3 tofacitinib RA development program is difficult to put into context with the rates published in the literature because the definition of what infections define the category 'opportunistic infections' is highly variable.

Most cases of esophageal candidiasis (5/7) were incidental findings during upper endoscopies; only one case, assessed as mild by the Principal Investigator, resulted in permanent discontinuation from study. Two of the 3 Pneumocystis jirovecii pneumonia cases occurred in Japan, a country where pneumocystis is diagnosed 10 times more frequently than in the United States. One death occurred due to Pneumocystis jirovecii pneumonia in a Japanese female patient. Of the 4 cases of CMV viremia/infections, 1 was CMV antigenemia without evidence of infection, 1 was a case of CMV found in association with an esophageal ulcer which resolved without antiviral therapy while tofacitinib treatment was continued, 1 was a case of CMV sialadenitis shown on biopsy, and 1 was a case of CMV hepatitis diagnosed by increased transaminases in the setting of CMV antigenemia. In this latter case, CMV was also detected in cerebrospinal fluid by PCR. Both cases of non-tuberculosis mycobacterial lung infections occurred in Japan. BK encephalitis was diagnosed in a critically ill patient with septic arthritis based on a positive polymerase chain reaction (PCR) test result for BK virus in cerebrospinal fluid; the patient improved with appropriate medical therapy. The 2 cases of cryptococcal pneumonia improved with appropriate medical management and the one case of cryptococcal meningitis resolved.

9.7.1.5. Other Infections of Interest

A review of the cumulative database for legionella or Listeria infections revealed only one case of legionellosis; no case of listeriosis has been reported in the combined Phase 2, 3 and LTE studies.

9.7.1.6. Monitoring and Management of Infections

Overall, the risk of infection and serious infection in RA patients treated with tofacitinib, dosed 5 or 10 mg BID is generally manageable with appropriate screening, monitoring and antimicrobial therapy when warranted.

Patients should be evaluated or tested for latent or active tuberculosis infection prior to initiating therapy with tofacitinib. Treatment of latent tuberculosis infection prior to treatment is recommended. Anti-tuberculosis therapy should also be considered prior to initiating treatment with tofacitinib in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection.

Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Patients should be closely monitored for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

As proposed in the draft label, tofacitinib should not be administered to patients with an active infection, including localized infections. Risks and benefits of therapy need to be weighed when considering the use of tofacitinib in patients with chronic or recurrent infection, who have been exposed to tuberculosis, with a history of serious or an opportunistic infection, who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, or with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with tofacitinib. Treatment with tofacitinib should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis until the infection is controlled. A patient who develops a new infection during treatment with tofacitinib should undergo a prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

9.7.2. Malignancies and Lymphomas/Lymphoproliferative Disorders

9.7.2.1. Overview of Malignancies (Excluding Non-Melanoma Skin Cancer), Including Lymphoma, Lung, and Breast

Certain types of cancers may occur in higher frequency in patients with RA, regardless of the treatment modality, including Hodgkin's and non-Hodgkin's lymphoma, leukemia, myeloma, and lung cancer (Khurana, 2008). In addition, malignancies, including lymphomas, are a concern with all therapeutic agents that treat RA by modulation of the immune system.

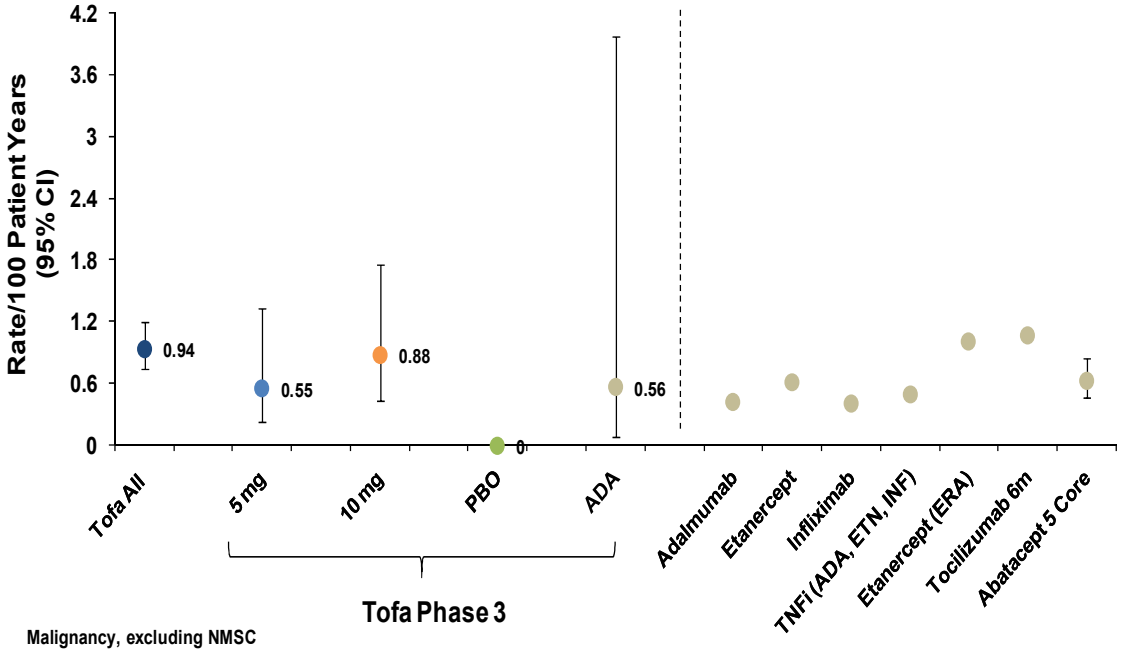
The incidence rate for all malignancies (excluding non-melanoma skin cancer [NMSC]), in RA patients treated with tofacitinib in the Phase 2, 3 and LTE studies was 0.939 events per 100 PYO, reported in 65 out of a total of 4791 tofacitinib treated patients (Table 45). The most common malignancies were lung cancer (16 patients) and breast cancer (11 patients). The incidence rate for malignancies, (excluding NMSC), in the LTE studies was 1.135 events per 100 PYO, which was slightly higher than in the Phase 3 RA studies (0.620 events/100 PYO). In both the Phase 3 and the LTE studies, the rate of malignancies for the 10 mg dose of tofacitinib was slightly higher than that for the 5 mg dose, although the confidence intervals (CIs) overlapped. Similar results were observed in tofacitinib patients on background DMARDs and monotherapy. One event of malignancy was reported for the adalimumab treatment group in the Phase 3 studies (out of 204 patients; IR of 0.559 events per 100 PYO) and 1 case (renal cell carcinoma) in the Phase 2 monotherapy Study 1035. Additonally, myelodysplastic syndrome was reported in one adalimumab-treated patient in the 1064/Standard study. This diagnosis was not confirmed by the central pathology laboratory over-read.

No cases of cancer were reported for placebo treated patients in the Phase 3 studies. It is important to note that placebo patients had less time in study compared with tofacitinib treated patients in the Phase 3 studies (202 total patient years of exposure for placebo patients compared with 2099 patient years of exposure for tofacitinib pateints).

Malignancy Rates Over Time

Overall, the point estimates, type of malignancy, and temporal distribution of malignancies remained consistent with clinical trial data reported for RA patients treated with TNF inhibitors and other biologic DMARDs (Table 45 and Figure 38) (Pallavicini, 2010; Carmona, 2010; Wolfe, 2007; Simon, 2009). Figure 39 shows the malignancy rates for the RA program over time, broken down into six month intervals. The distribution of malignancies occurring over time appears relatively uniform; there is no clear temporal relationship to the occurrence of any specific type of malignancy. The event rate seems to be slightly higher in the last period, however the number of patients exposed is smaller and the confidence intervals are wide.

Figure 38. Malignancy (excluding NMSC) Incidence Rates (95% CI) for Tofacitinib versus Clinical Trial Data for TNF Inhibitors and Other Biologic DMARDs

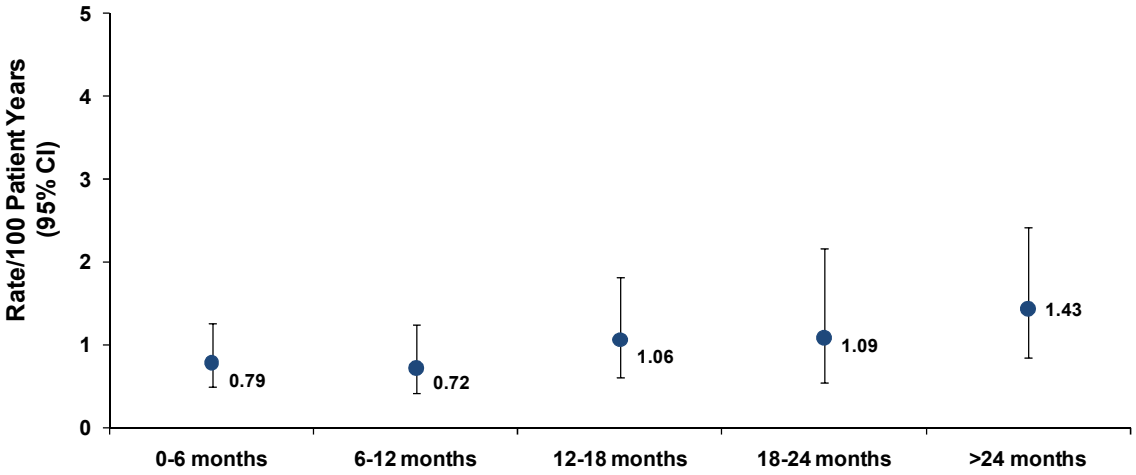


Malignancy, excluding NMSC
Bars indicate 95% Confidence Limits.
Dots alone represent point estimates found in different published

5 mg=tofacitinib 5 mg twice daily; 10 mg=tofacitinib 10 mg twice daily; ADA=adalimumab; DB=double blind studies; DMARDs=disease modifying antirheumatic drugs; ERA=early rheumatoid arthritis clinical trial; ETN=etanercept; INF=infliximab; LT=long term studies; MA=meta-analysis; NMSC=non-melanoma skin cancer; OL=open label studies; PBO=placebo; PYO=patient years of observation;RCT=randomized control trial; TNF=tumor necrosis factor; TNFi=tumor necrosis factor inhibitors; Tofa All=tofacitinib data from Phase 2, Phase 3, and LTE studies; Tofa Phase 3=tofacitinib Phase 3 studies that include the treatment groups of: 5 mg=tofacitinib 5 mg BID; 10 mg=tofacitinib 10 mg BID, PBO=placebo, ADA=adalimumab; Tocilizumab 6m=tocilizumab studies of 6 month duration
References:TNFi=tumor necrosis factor inhibitors data extracted from Askling, 2010; Adalimumab=adalimumab data extracted from Abbott Laboratories, Humira, 2011; Askling, 2010; Etancercept RCT MA=etancercept randomized control trial meta-analysis data extracted from Askling, 2010; Etanercept ERA CT=etanercept early rheumatoid arthritis clinical trial data extracted from Amgen Inc., 2011;

Infliximab=infliximab data extracted from Askling, 2010; Tocilizumab 6m=tocilizumab 6 month data extracted from U.S. FDA Drug Approval Package, Actemra, 2010; Abatacept 5 core=data from 5 randomized controlled trials in abatacept development program extracted from Simon, 2009.

Figure 39. Incidence Rates of Malignancies (Excluding NMSC) Over Time in Tofacitinib Patients, Phase 2, Phase 3, and LTE RA Studies



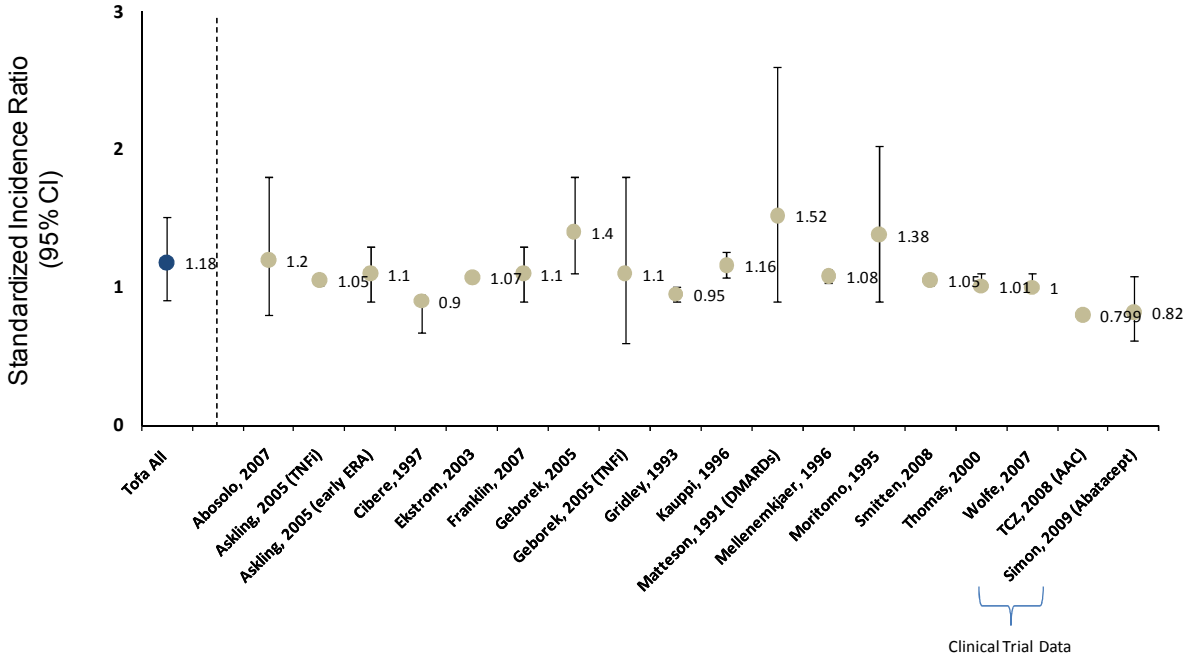
Months	0-6 months	6-12 months	12-18 months	18-24 months	>24 months
Patients	4791	4012	3126	2054	941
Patient-years	2166.00	1810.96	1229.13	736.74	976.04
Patients with Events	17	13	13	8	14

CI=confidence interval; LTE=long term extension; NMSC=non-melanoma skin cancer; RA=rheumatoid arthritis
Patient exposure time is counted from first dose of tofacitinib in the index study through last known dose in the extension study. Some events may have occurred post end of treatment, these events were counted in the numerator and patients' full tofacitinib treatment exposure was included in denominator. Data as of 29 September 2011

Standardized Incidence Ratios

Malignancy data from the tofacitinib RA development program were further evaluated by estimation of the standardized incidence ratios (SIRs) based on comparison with the Surveillance Epidemiology and End Result (SEER) United States database. The SIR for overall malignancies (excluding NMSC) in the tofacitinib program, normalized for age and gender to the U.S. general population, was 1.18, demonstrating no difference from the U.S. population (Table 45) This SIR is also consistent with reported ratios from observational data for TNF inhibitors and other biologic DMARDs (Figure 40).

Figure 40. Malignancy (excluding NMSC) Standardized Incidence Ratios (95% CI) for Tofacitinib versus Clinical Trial and Observational Data* for TNF Inhibitors and Other Biologic DMARDs



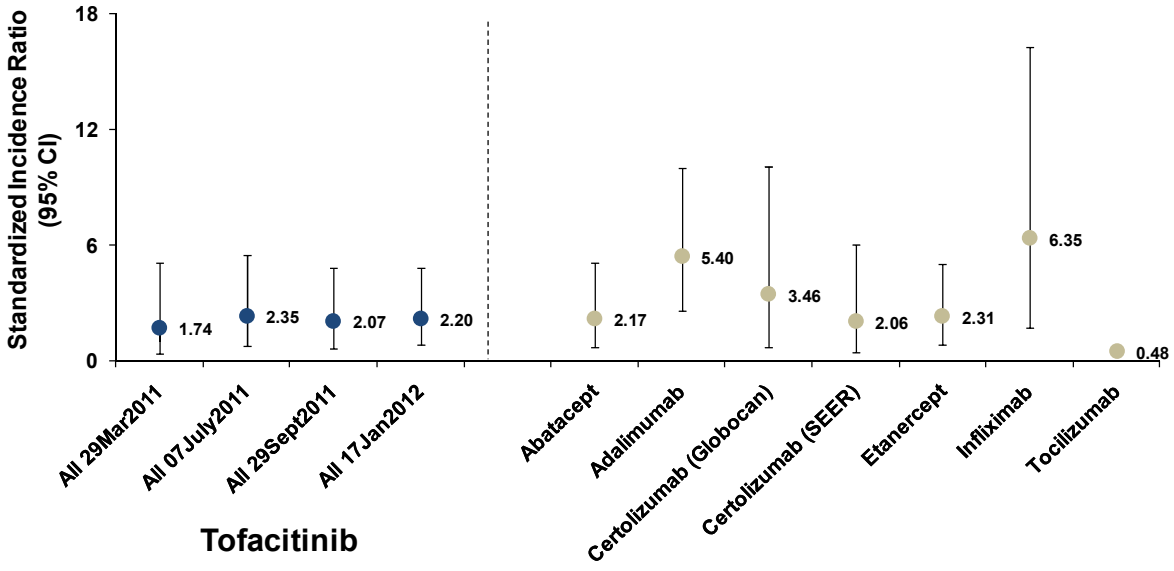
Bars indicate 95% confidence limits
Comparator data for the standardized incidence ratios (SIRs) is from observational sources, not clinical trial data, as the duration of clinical trials are typically not adequate to provide sufficient malignancy data to calculate SIRs.
DMARDs=disease modifying antirheumatic drugs; SIR=standardized incidence ratio; TNF=tumor necrosis factor; TNFi=tumor necrosis factor inhibitors; Tofa All=tofacitinib data from Phase 2, Phase 3, and LTE studies
Explanations of external comparator data referenced in figure:Abasolo: 789 randomly selected RA pts vs. general population (Spain); Askling: 3 RA cohorts (one prevalent, admitted to hospital 1990-2003; one incident, diagnosed 1995-2003; one treated with TNF antagonists 1999-2003) vs. entire Swedish population; Cibere: prospective cohort of 862 pts w/RA at the University of Saskatchewan Rheumatic Disease Unit vs. provincial cancer statistics (Canada); Ekstrom: patients hospitalized with RA vs. general Swedish population; Franklin: persons with inflammatory polyarthritis within a large primary care-based register in the UK vs. regional population; Geborek: South Swedish Arthritis Treatment Group Register (757 etancerpt or infliximab tx & 800 conventional tx) vs. general population registers; Gridley: patients with an inpatient diagnosis of RA vs. Swedish population; Kauppi: Finnish cohort using National discharge register, cancer register vs. general Finnish pop register; Matteson: Patients with RA enrolled in azathioprine registry (RAAR) vs. Canadian census and cancer data; Mellemkjaer: Patients with RA within the Danish Hospital Discharge Register vs. Danish population; Moritomo: Consecutive RA patients living in Osaka and treated at one center vs. general population in Osaka (Japan); Thomas: Scottish inpatient records with RA diagnosis vs. national cancer incidence rates in Scotland; Wolfe: Participants in the US National Data Bank for Rheumatic Diseases vs. SEER (US);
References: Smitten, 2008 US FDA Tocilizumab Drug Approval Package, 2010; US FDA Tocilizumab Advisory Committee, 2010; Simon, 2009.

9.7.2.1.1. Lymphoma

A total of 6 cases of lymphoma were reported for tofacitinib patients in the RA program with an estimated total of 9070.58 patient years of exposure, yielding and IR estimate of 0.066 events per 100 PYO, as of 17 January 2012 (Table 45). There were no cases of lymphoma in the placebo or adalimumab groups. There is no apparent pattern of occurrence based on either tofacitinib dose or duration of therapy. Published lymphoma IRs for RA patients treated with nonbiologic and biologic DMARDs range from 0.06 to 0.140 events per 100 PYO.

In the tofacitinib trials, the SIR for lymphoma, normalized for age and gender to the U.S. general population, has ranged between 1.74 and 2.35, based on periodic monitoring during the development program. These SIRs for lymphomas have remained stable during the RA program and are consistent with those reported in RA clinical trials of TNF inhibitors and other biologic DMARDs (Figure 41).

Figure 41. Lymphoma Standardized Incidence Ratios for Tofacitinib During the RA Program versus Published Standardized Incidence Ratios of Biologic DMARDs



Data as of 17 January 2012
29 March 2011=cut-off date for NDA submission. 29 September 2011=cut-off date for 4 month safety update report
All=data for tofacitinib 5 mg and 10 mg BID doses form Phase 2, Phase 3, and LTE studies; DMARDs=disease modifying antirheumatic drugs; SIR=standardized incidence rate;TNF=tumor necrosis factor;TNFi=tumor necrosis factor inhibitors
References:Abatacept=abatacept date extracted from Simon, 2009; Adalimumab=adalimumab data extracted from U.S. FDA Drug Briefings, Safety of TNF-Blocking Agents; Certolizumab (Globocan)=certolizumab data extracted from UCB, Inc. Cimzia Safety Information, 2011; Certolizumab (SEER)=certolizumab surveillance, epidemiology and end results data extracted from UCB, Inc. Cimzia Safety Information, 2011; Etanercept=etanercept data extracted from U.S. FDA Arthritis Advisory Committee Meeting Briefing Document, Enbrel (etanercept). Infliximab=infliximab data extracted from U.S. FDA Drug Briefings, Safety of TNF-Blocking Agents; Tocilizumab=tocilizumab data extracted from U.S. FDA Drug Approval Package, Actemra, 2010.

The types of lymphomas reported in the RA development program were consistent with lymphomas described in the RA population and general population (Gonzalez, 2007; Bjornadal, 2002; Gottlieb, 2011). Persons with RA are at increased risk of developing lymphoma compared with the general population, which may be related to both immunosuppressive therapy and RA severity. Some lymphomas in RA patients arise in B-cells, in association with latent EBV infection and some regress with reduction in immunosuppressive therapy (Abasolo, 2008; Ekstrom, 2003; Wolfe, 2007; Franklin, 2007; Geborek, 2005; Wolfe, 2004). It is not clear whether the risk of lymphoma is increased further by methotrexate or TNF inhibitor agents, though some studies have concluded that the use of DMARDs was not associated with lymphoma risk (Baecklund, 2004; Baecklund, 2006). Baecklund, et al, concluded that a high level RA disease activity coupled with a long duration of disease is associated with a greater risk of lymphoma. The role of JAK inhibition in the development of malignancy is not known.

Table 42. Summary of Lymphoma/Lymphoproliferative Disorder in Tofacitinib Rheumatoid Arthritis Clinical Studies as of 17 January 2012*

Diagnosis (EBV tissue status)	**Demographics**	**Duration of Therapy at Onset**	**tofacitinib Dose**† (background drug)	**Organ(s) Affected**	**Country**
Primary CNS lymphoma (EBV negative)	78 year old White Female	818 days	5 mg BID (MTX)	Brain	Spain
Lymphoproliferative disorder (EBV positive)	51 year old Asian Female	227 days	5 mg BID	Abdominal lymph nodes	Japan
Lymphoma (EBV test showed IgG:+/- and non-specific EBNA fluorescence positive as infection-free or weak response of infection)	47 year old Asian Female	220 days	10 mg BID (MTX)	Thymus	Japan
Diffuse large B-cell lymphoma (EBER + in only rare, scattered mononuclear cells)	69 year old Caucasian Female	642 days	10 mg BID (MTX)	Left breast, media-stinum, and left axillary area	United States
High grade B-cell Burkitt-like lymphoma (EBER stain is positive in a small focus of cells)	65 year old Caucasian Male	149 days	10 mg BID	Right submandibular gland-right neck	New Zealand

Table 42. Summary of Lymphoma/Lymphoproliferative Disorder in Tofacitinib Rheumatoid Arthritis Clinical Studies as of 17 January 2012*

Diagnosis (EBV tissue status)	Demographics	Duration of Therapy at Onset	tofacitinib Dose† (background drug)	Organ(s) Affected	Country
T-cell chronic lymphocytic leukemia (EBV negative)	63 year old Caucasian Male	449 days	Blinded Therapy (assume Tofacitinib/MTX)	Hematologic	Czech Republic

Data as of 17 January 2012
AER=adverse event report number; EBER=Epstien Barr encoded ribonucleic acid; EBNA=Epstein Barr nuclear antigen; EBV=Epstein Barr virus; IgG=immunoglobulin G; MTX=methotrexate
* One additional case was reported in the LTE 1024/Sequel study after the 17 January 2012 date; this case is not included in the incidence rate calculations.
† Randomized treatment assignment

9.7.2.1.1.1. Occurrence of Post Transplant Lymphoproliferative Disorder/Lymphoma in Tofacitinib Renal Transplant Studies

In contrast to the lymphoma IR observations in the RA development program, an increased rate of post transplant lymphoproliferative disorder (PTLD) was observed in renal transplant patients treated with tofacitinib in transplant study A3921030 and its extension study A3921050, compared with the general renal transplant population. The overall PTLD incidence proportion was 5/218 (2.3%) which exceeds the incidence typically reported in renal transplant patients (approximately 0.5%-1%) (Caillard, 2005; Caillard, 2006).

There are significant differences between the intensity and complexity of immunosuppressive regimens used in the tofacitinib renal transplant program and the tofacitinib RA program. In contrast to the use of multiple immunosuppressive drugs in the transplant program, (tapering doses of glucocorticoids, mycophenolate products and induction therapy with anti-IL-2 monoclonal antibodies), patients with RA received tofacitinib either as monotherapy or in combination with stably-dosed traditional DMARDs that are not potent immunosuppressives, e.g., MTX (weekly dose ≤25 mg). Approximately half of the RA patients were treated with low-dose corticosteroids (daily dose ≤10 mg prednisone equivalent).

Analysis of the 5 PTLD cases in these two transplant studies indicated that tofacitinib exposure above the median time-weighted plasma level over the first 6 months post-transplant is associated with the risk of developing PTLD. PTLD has not been observed in patients who had tofacitinib exposure below the median in the first 6 months post-transplant. Over-immunosuppression in patients with high exposure to tofacitinib administered in combination with multiple immunosuppressive drugs during the first 6 months post-transplant, may at least partially explain an increased risk of lymphoma. No relationship was identified between drug concentration and occurrence of malignancies or lymphoma in the RA population.

9.7.2.1.1.2. Occurrence of Lymphoma in Non-Clinical Studies

At necropsy, tumors considered to be lymphomas were observed in 3 of 8 monkeys in the adult 39-week monkey study. No lymphomas were observed in the 39-week juvenile monkey study at the same doses and at similar exposures as in adult monkeys (0 of 18 monkeys).

Treatment-related lymphomas were observed in 3 of 8 high dose (5 mg/kg BID, 10 mg/kg/day) animals in the 39-week monkey study. Two of the 3 lymphomas from the 39-week monkey study were B cell lymphomas and positive for lymphocryptovirus (LCV) by immunohistochemical (EBNA-2) and in situ hybridization (EBER-1) staining. LCV is the term for the Epstein-Barr (EBV)-like gamma herpes virus in cynomolgus monkeys (Carville, 2008). The remaining monkey had a lymphoma in the peri-thymic fat which was determined to be a T cell lymphoma based on immunohistochemical staining.

Chronic immunosuppression in monkeys may be associated with the development of lymphomas. LCV associated B cell lymphomas were not unexpected and were similar to the LCV/EBV positive B cell lymphomas observed with PTLD cases in nonhuman primates (McInnes, 2002; Schmidtko, 2002) and humans (Swerdlow, 2008). Therefore, the LCV-associated lymphomas observed in the 39-week monkey study were considered secondary to immunosuppression.

9.7.2.1.2. Lung Cancer

The overall incidence rate for lung cancer in tofacitinib patients for the Phase 2, Phase 3, and LTE studies was 0.231 events per 100 PYO (Table 43). This includes 16 patients with lung cancer out of a total of 4791 of tofacitinib patients. Five cases of lung cancer occurred within 6 months of initiating tofacitinib therapy. Given the known growth rate of solid tumors it is highly likely these lung cancers were pre-existent prior to tofacitinib therapy. There was 1 case of lung cancer in the adalimumab treatment group in Phase 3 studies (IR=0.559 events per 100 PYO). There was an additonal patient who was treated with adalimimub for 1 year in the 1064/Standard study before entering an LTE study where the patient started tofacitinib therapy; lung cancer was diagnosed after 110 days on tofacitinib treatment and included in the incidence rate calculations for tofacitinib. As this patient was treated with both adalimumab and tofacitinib, inclusion of this patient in the adalimumab group would increase the overall incidence rate for lung cancer for adalimumab.

Of the 16 patients with lung cancer, 13 were non-small cell lung cancer (NSCLC) and 3 were small cell lung cancer (SCLC); 1 patient in Japan had both metastatic SCLC and NSCLC (bronchoalveolar cell cancer). There was also 1 case of lung cancer, histology unspecified, in a patient who never smoked. The lung cancers that occurred in this development program are consistent with the type of lung cancer observed for this demographic in patients with moderate to active RA (Simon, 2009). Addtionally, 9 were current smokers, 4 were ex-smokers, and 3 had never smoked. For the current and ex-smoker patients with lung cancer, the mean (range) duration of smoking was 40 (20-54) years. The incidence rate of lung cancer in the RA program is consistent with the published literature of RA patients treated with non-biologic and biologic DMARDs (Table 45)

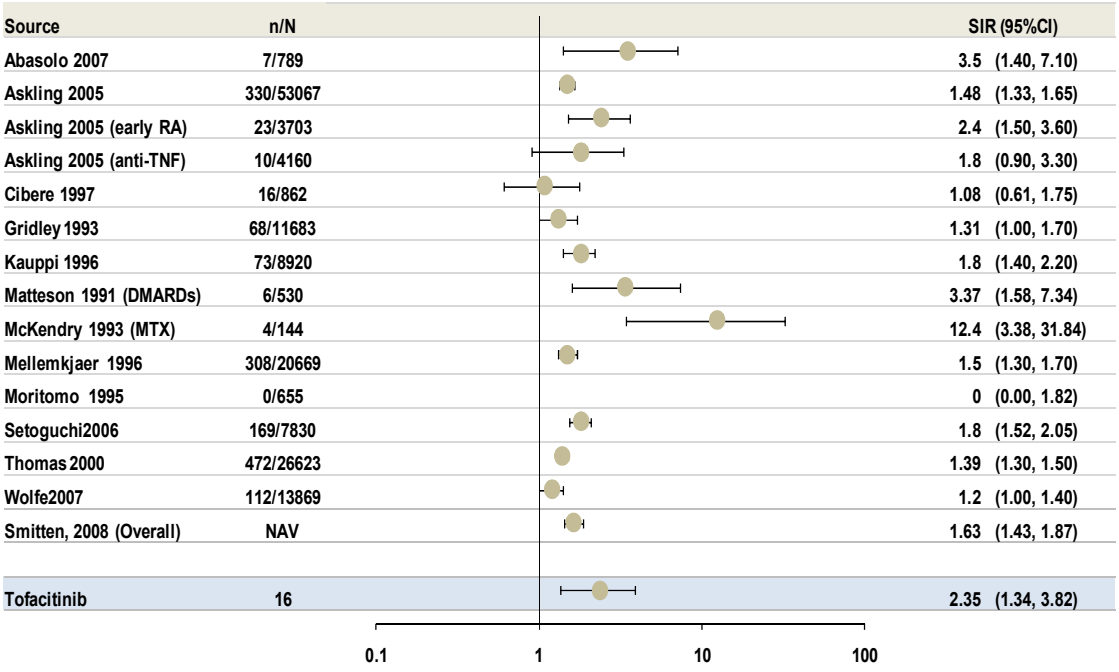
Table 43. Incidence Rates of Lung Cancer in Phase 2, Phase 3, and Long Term Extension Studies, Tofacitinib Treatment Groups

		Tofacitinib		
Population		**5 mg BID**	**10 mg BID**	**All Doses**
P2P3LTE	Total no. patients	-	-	4791
	No. (%) patients with events	-	-	16 (0.33)
	Exposure for event (pt-yr)	-	-	6921.5
	Incidence rate, in events per 100 pt-yr (95% CI)	-	-	0.231 (0.142, 0.377)
LTE	Total no. patients	1370	2145	3515
	No. (%) patients with events	4 (0.29)	8 (0.37)	12 (0.34)
	Exposure for event (pt-yr)	2725.8	1683.5	4409.4
	Incidence rate, in events per 100 pt-yr (95% CI)	0.147 (0.055, 0.391)	0.475 (0.238, 0.950)	0.272 (0.155, 0.479)

Data as of 29 September 2011
BID=twice daily; CI=confidence interval; LTE=long term extension studies; P2P3LTE=Phase 2, Phase 3, and long term extension studies; pt-yr=patient-years.
Patients' exposure time is counted from first dose of tofacitinib in the index study through last known dose in the extension study.
Some events may have occurred after the end of treatment: these events were counted in the numerator and patients' full tofacitinib treatment exposure was included in denominator.

The SIR for lung cancer as compared with the SEER database is 2.35; although elevated compared with the general United States population, the SIR is consistent with SIRs from published literature for patients with RA (Figure 42).

Figure 42. Lung Cancer Standardized Incidence Ratio in Tofacitinib* is Consistent with Standardized Incidence Ratios of TNF Inhibitors and other Biologic DMARDs



CI=confidence interval; DMARDs=disease-modifying anti-rheumatic drugs; RA=rheumatoid arthritis; TNF=tumor necrosis factor; MTX=methotrexate; SIR=standardized incidence rate

*Number of SEER-defined malignancies in tofacitinib group as of 29 September 2011 was 16
SEER data were used as the comparator for the tofacitinib SIRs
Abasolo: 789 randomly selected RA pts vs. general population (Spain)
Askling: 3 RA cohorts (one prevalent, admitted to hospital 1990-2003; one incident, diagnosed 1995-2003; one treated with TNF antagonists 1999-2003) vs. entire Swedish population
Cibere: prospective cohort of 862 pts w/RA at the University of Saskatchewan Rheumatic Disease Unit vs. provincial cancer statistics (Canada)
Gridley: patients with an inpatient diagnosis of RA vs. Swedish population
Kauppi: Finnish cohort using National discharge register, cancer register vs. general Finnish pop register
Matteson: Patients with RA enrolled in azathioprine registry (RAAR) vs. Canadian census and cancer data
Mellemkjaer: Patients with RA within the Danish Hospital Discharge Register vs. Danish population
Moritomo: Consecutive RA patients living in Osaka and treated at one center vs. general population in Osaka (Japan)
Setoguchi: Administrative claims dbs from US (NJ and PA) & Canada (BC) vs. SEER
Thomas: Scottish inpatient records with RA diagnosis vs. national cancer incidence rates in Scotland
Wolfe: Participants in the US National Data Bank for Rheumatic Diseases vs. SEER (US)
Abasolo, 2007; Askling, 2005-2; Cibere, 1997; Gridley, 1993; Kauppi, 1996; Matteson, 1991; McKendry, 1993; Mellemkjaer, 1996; Moritomo, 1995; Setoguchi, 2006; Thomas, 2000; Wolfe, 2007.
Additional source for comparator data: Smitten, 2008

9.7.2.1.3. Breast Cancer

The overall incidence rate for breast cancer in tofacitinib treated patient in the Phase 2, Phase 3, and LTE studies was 0.191 events per 100 PYO (Table 44 and Table 45). This includes 11 patients with breast cancer out of a total of 4011 female patients. There were no cases of breast cancer in the placebo or adalimumab treatment groups.

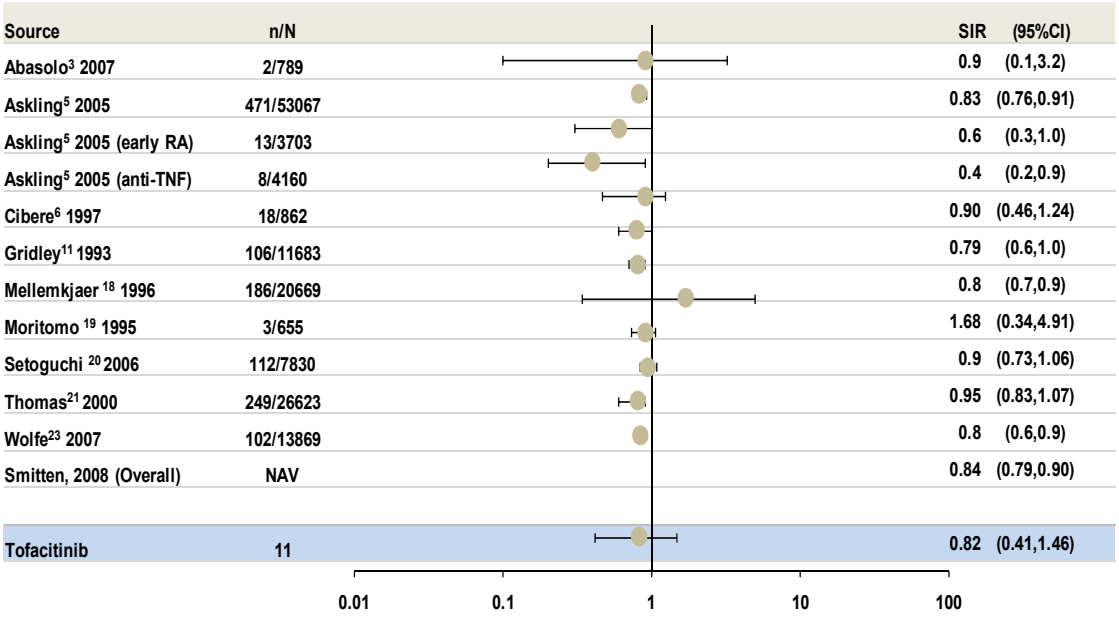
Table 44. Incidence Rates of Breast Cancer in Tofacitinib Patients, Phase 2, Phase 3, and Long Term Extension Studies

Population		Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses
P2P3LTE	Total no. patients (women only)	-	-	4011
	No. (%) patients with events	-	-	11 (0.27)
	Exposure for event (pt-yr)	-	-	5759.7
	Incidence rate, in events per 100 pt-yr (95% CI)	-	-	0.191 (0.106, 0.345)
LTE	Total no. patients	1143	1774	2917
	No. (%) patients with events	6 (0.52)	2 (0.11)	8 (0.27)
	Exposure for event (pt-yr)	2258.49	1400.85	3659.34
	Incidence rate, in events per 100 pt-yr (95% CI)	0.266 (0.119, 0.591)	0.143 (0.036, 0.571)	0.219 (0.109, 0.437)

BID=twice daily; CI=confidence interval; LTE=long term extension studies; P2P3LTE=Phase 2, Phase 3, and long term extension studies; pt-yr=patient-years.
Some events may have occurred after the end of treatment; these events were counted in the numerator and patients' full treatment exposure was included in denominator.

The incidence rate of breast cancer in the tofacitinib RA program is consistent with the published literature for RA patients treated with DMARDs (Table 45). The SIR for breast cancer as compared with the SEER database is consistent with the general U.S. population estimates and SIRs in patients with RA treated with TNF inhibitors and other biologic DMARDs (Figure 43).

Figure 43. Breast Cancer Standardized Incidence Ratio in Tofacitinib* (Female Patients) is Consistent with Standardized Incidence Ratios of TNF Inhibitors and other Biologic DMARDs



CI=confidence interval; DMARDs=disease-modifying anti-rheumatic drugs; RA=rheumatoid arthritis; TNF=tumor necrosis factor; MTX=methotrexate; SIR=standardized incidence rate

*Number of SEER-defined malignancies in tofacitinib group as of 29 September 2011 was 11
SEER data were used as the comparator for the tofacitinib SIRs
Abasolo: 789 randomly selected RA pts vs. general population (Spain)
Askling: 3 RA cohorts (one prevalent, admitted to hospital 1990-2003; one incident, diagnosed 1995-2003; one treated with TNF antagonists 1999-2003) vs. entire Swedish population
Cibere: prospective cohort of 862 pts w/RA at the University of Saskatchewan Rheumatic Disease Unit vs. provincial cancer statistics (Canada)
Gridley: patients with an inpatient diagnosis of RA vs. Swedish population
Mellemkjaer: Patients with RA within the Danish Hospital Discharge Register vs. Danish population
Moritomo: Consecutive RA patients living in Osaka and treated at one center vs. general population in Osaka (Japan)
Setogucchi:Administrative claims dbs from US (NJ and PA) & Canada (BC) vs. SEER
Thomas: Scottish inpatient records with RA diagnosis vs. national cancer incidence rates in Scotland
Wolfe: Participants in the US National Data Bank for Rheumatic Diseases vs. SEER (US)
Additionasl source for comparator data: Smitten, 2008

Incidence rates and SIRs for all malignancies (excluding NMSC), lymphoma, lung cancer and breast cancer compared with biologic DMARDs are presented in Table 45.

Table 45. IRs and SIRs for All Malignancies (Excluding NMSC), Lymphoma, Lung, and Breast Cancer, for Tofacitinib Patients versus TNF Inhibitors and other Biologic DMARDs

	Incidence Rate Tofacitinib Patients Events/100 PYO (95% CI) N=4791	Incidence Rate TNF inhibitors/ Biologic DMARDs* Events/100 PYO	Standardized Incidence Ratio Tofacitinib Patients† (95% CI) N=4791	Standardized Incidence Ratio TNF inhibitors/ Biologic DMARDs‡
All malignancies (excluding NMSC)	0.939 (0.737, 1.198)	0.3-1.77[a]	1.18 (0.91, 1.51)	0.9-1.1[d]
Lymphoma	0.066 (0.030, 0.147)	0.06-0.140[b]	2.20 (0.81, 4.79)	1.1-9.7[e]
Lung	0.231 (0.142, 0.377)	0.228-0.26[c]	2.35 (1.34, 3.82)	1.08-3.5[f]
Breast	0.191 (0.106, 0.345)	0.11-0.34[c]	0.82 (0.41, 1.46)	0.4-1.68[f]

Data as of 29 September 2011, except lymphoma data as of 17 January 2012
CI=confidence interval; DMARD=disease modifying anti-rheumatic drug; IR=incidence rate; NMSC=nonmelanoma skin cancer; PYO=patient years of observation; RA=rheumatoid arthritis; SIR=standardized incidence ratio as compared with the Surveillance Epidemiology and End Result database
* IRs from randomized clinical trial data
† Including cases in ongoing studies (Studies 1044 [post M-12] and 1069) using updated exposure estimates for these studies
‡ SIRs from published observational data
[a] Pallavicini, 2010; Carmona, 2010; Wolfe, 2007; Simon, 2009
[b] United States National Data Bank for Rheumatic Diseases; Wolfe, 2007; Simon, 2009
[c] United States National Data Bank for Rheumatic Diseases and cohorts of RA patients treated with DMARDs
[d] Surveillance Epidemiology and End Result (SEER) database (US General Population), Howlader, 2011.
[e] Kinlen, 1992; Gridley, 1993; Mellemkjaer, 1996; Kauppi, 1997; Thomas, 2000; Ekström, 2003; Mariette, 2002; Wolfe, 2007; Parikh-Patel, 2009.
[f] Smitten, 2008

9.7.2.2. Non-Melanoma Skin Cancer

Increased risk for the development of NMSC is reported in patients with RA, as well as with the use of TNF inhibitors and prednisone (Askling, 2005; Mellemkjaer, 1996; Chakravarty, 2005). A total of 31 out of 4791 patients treated with tofacitinib in the Phase 2, 3, and LTE studies reported NMSC, resulting in an overall IR of 0.450 events per 100 PYO. Based upon available information, the NMSC events primarily occurred in sun-exposed areas of the body including the face/head and hands. This rate is consistent with the IR observed in patients with RA treated with biologic DMARDs, which ranges from 0.17 to 1.81 events per 100 PYO (Wolfe, 2007; Chakravarty, 2005; Askling, 2010). The IR for NMSC was 0.569 events per 100 PYO in the LTE studies. In the LTE studies, the IR for the 10 mg dose group (0.894 events per 100 PYO) was higher than that for the 5 mg dose group (0.368 events per 100 PYO), although the CIs overlapped.

9.7.2.3. Malignancies in Population Subsets

The total number of malignancies across the RA program was not large. Therefore, the examination of differences in the rates of malignancies or of specific cancer types in subpopulations is difficult and primarily qualitative.

As expected, patients ≥ 65 years of age had higher incidence rate point estimates for malignancies than younger patients and males tended to have higher rates than females in the tofacitinib RA program. Published information indicates that the incidence of solid cancers in patients with RA increases with age and older males (age 50-74 years, and ≥ 75 years) have a higher incidence of solid cancers than females in the same age ranges (Askling, 2005).

9.7.2.4. Deaths Due to Malignancies

There were 11 deaths due to malignancies in tofacitinib treated patients in the Phase 2, 3, and LTE studies as of 29 September 2011. Five deaths were due to lung cancer (3 patients receiving 5 mg tofacitinib, 2 patients receiving 10 mg tofacitinib), and 1 death each due to breast cancer, colon cancer, ovarian cancer, gallbladder cancer, and synovial sarcoma (all receiving 5 mg tofacitinib), and 1 death in a patient with hepatic and lung cancer receiving 10 mg tofacitinib. There was one death in the adalimumab group due to lung cancer.

9.7.2.5. Conclusions for Malignancies and Lymphomas

The pattern, types, incidence rates, and standardized incidence ratios of malignancies and lymphomas observed in the tofacitinib RA development program were consistent with the type, distribution, and rates of malignancies and lymphomas expected for this demographic in patients with moderately to severely active RA. While the potential role of Janus kinase inhibition in the development of malignancies is not known, current data from the tofacitinib RA program, including the LTE studies, have not identified a clear link between this compound and development of malignancies. Planned pharmacovigilance activities for malignancies and lymphomas include long term active surveillance utilizing US and European registries and continuation of the LTE studies post-approval.

9.7.3. Cardiovascular Events, Blood Pressure Changes, and Lipid Increases

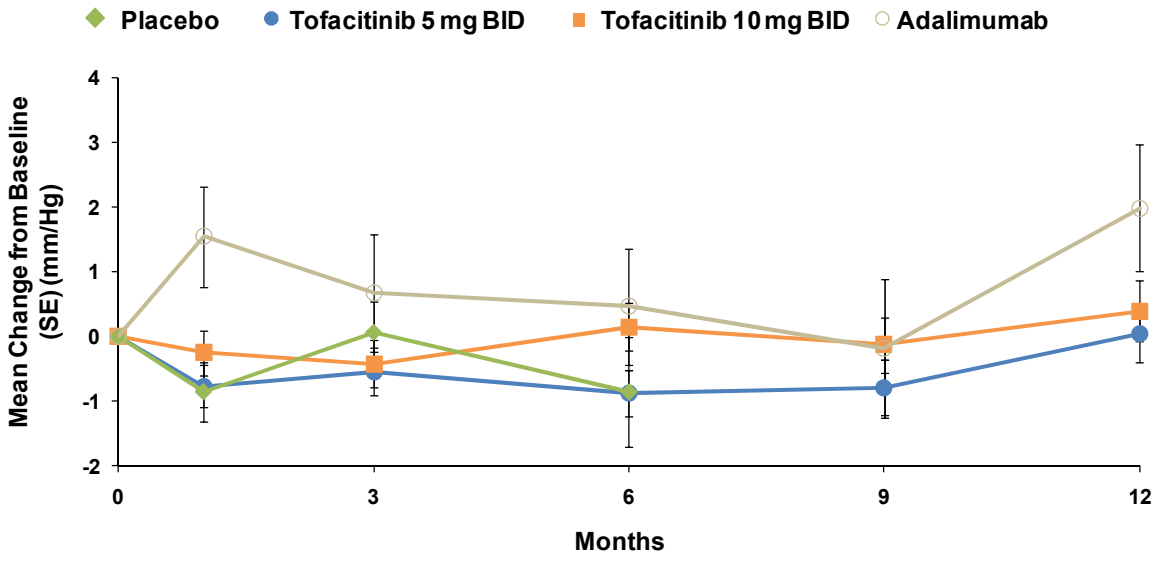
A comprehensive evaluation of the Phase 2 and 3 and LTE safety data was undertaken to assess CV risk in the program, including evaluation of possible blood pressure changes, lipid changes and CV event rate. Also, to better understand the cardiovascular (CV) safety profile of tofacitinib, cardiovascular events and deaths were adjudicated by an independent, blinded committee.

9.7.3.1. Blood Pressure Changes

9.7.3.1.1. Blood Pressure

There is no clear association between tofacitinib therapy and clinically meaningful increases in blood pressure (Figure 44 and Figure 45). Baseline mean systolic BP (SBP) was comparable in all treatment groups. Changes from baseline in BP were small in all treatment groups during the first 3 months of treatment. Both SBP and DBP remained stable following treatment for up to 12 months in the tofacitinib treatment groups in the Phase 3 studies and during the LTE studies up to 27-30 months. In the tofacitinib 10 mg group in the LTE studies, both SBP and DBP also remained stable or decreased slightly up to 18 months of follow-up.

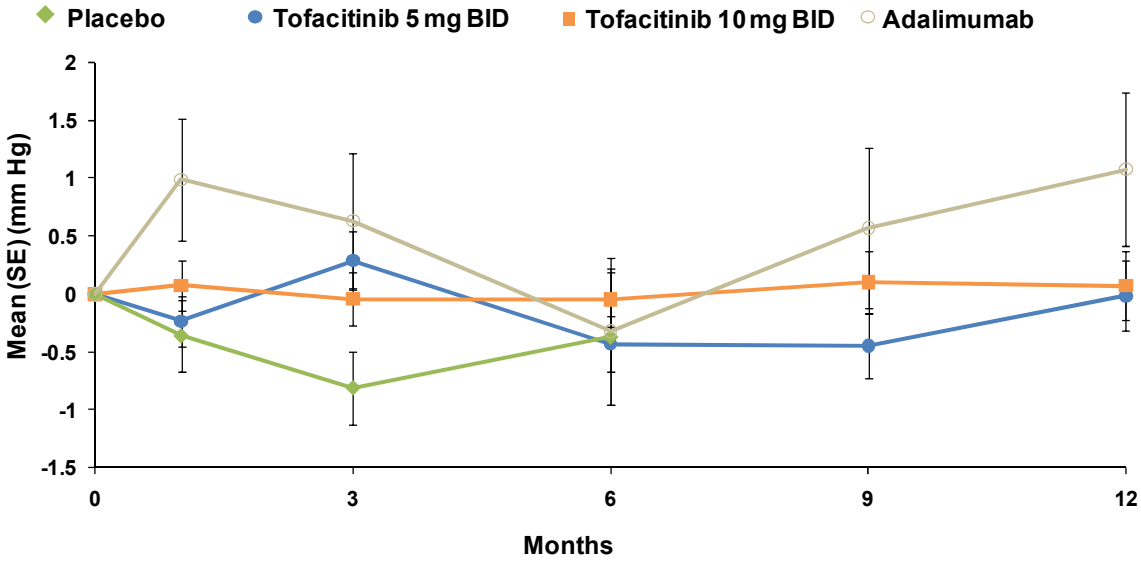
Figure 44. Mean (± SE) Change From Baseline Systolic Blood Pressure (mm Hg) per Visit in All Phase 3 Studies (0 to 12 Months)



Mean (± SE) Percent Change From Baseline Systolic Blood Pressure (mm Hg) per Visit in All Phase 3 Studies (0 to 12 Months)

BID=twice daily; mm/Hg=millimeters of mercury; SE=standard error

Figure 45. Mean (± SE) Change From Baseline Diastolic Blood Pressure (mm Hg) per Visit in All Phase 3 Studies (0 to 12 Months)

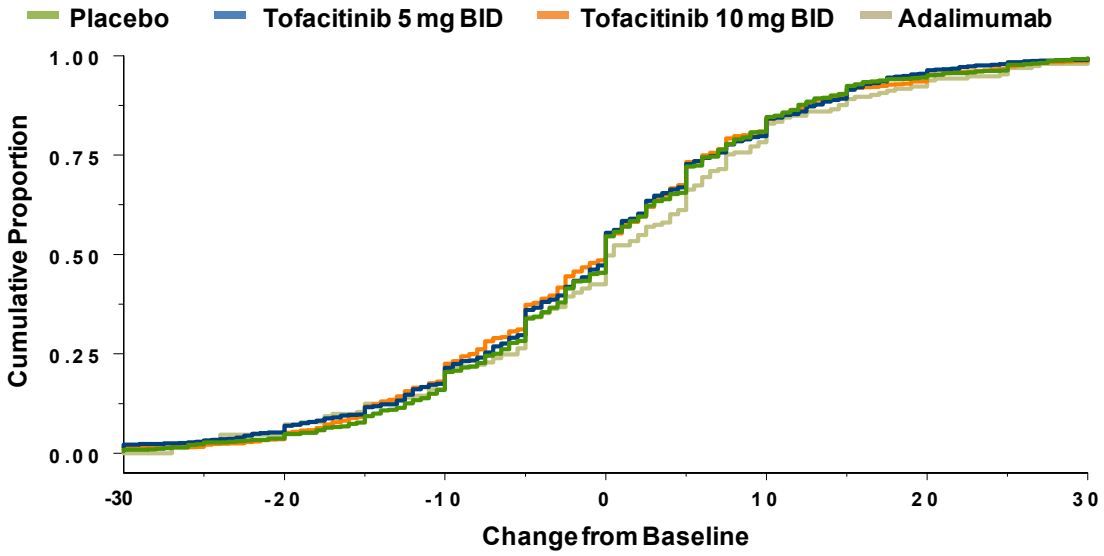


BID=twice daily; q2w=every 2 weeks; SC=subcutaneous; SE=standard error.

9.7.3.1.2. Blood Pressure Cumulative Frequency Distributions

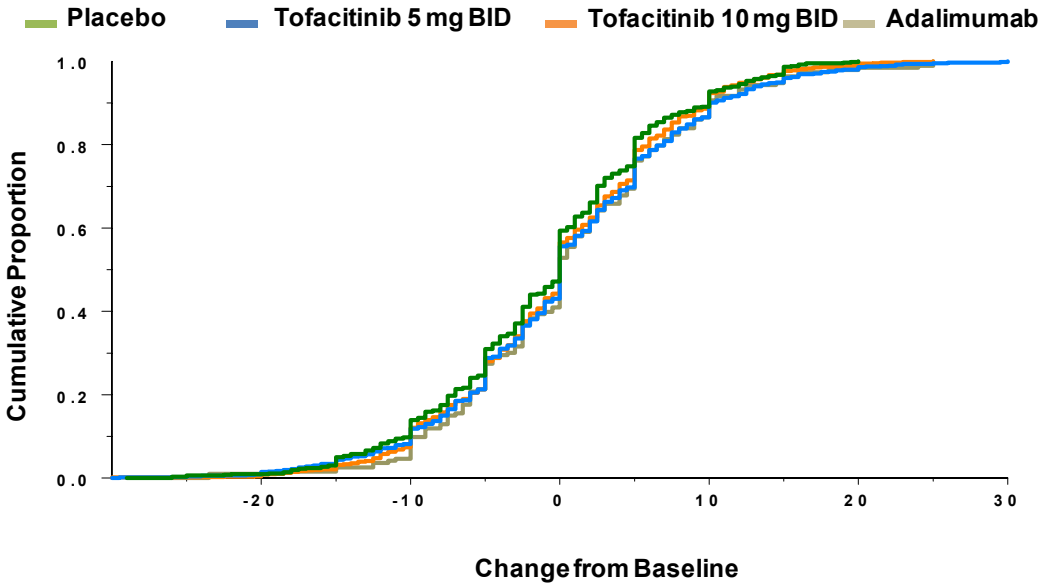
The cumulative frequency distributions of SBP, DBP and their changes across the different treatment groups during the first 3 months of treatment were nearly superimposable (Figure 46 and Figure 53). These data, in combination with the lack of tofacitinib effect on mean changes in BP indicate that tofacitinib has no clinically meaningful effects on blood pressure.

Figure 46. Cumulative Frequency Distribution of Change from Baseline in Systolic Blood Pressure (mm Hg) at Month 3 Visit - All Phase 3 Studies (Up to 3 Months)



BID=twice daily

Figure 47. Cumulative Frequency Distribution of Change from Baseline in Diastolic Blood Pressure (mm Hg) at Month 3 Visit - All Phase 3 Studies (Up to 3 Months)



BID=twice daily

9.7.3.1.3. Summary for Blood Pressure

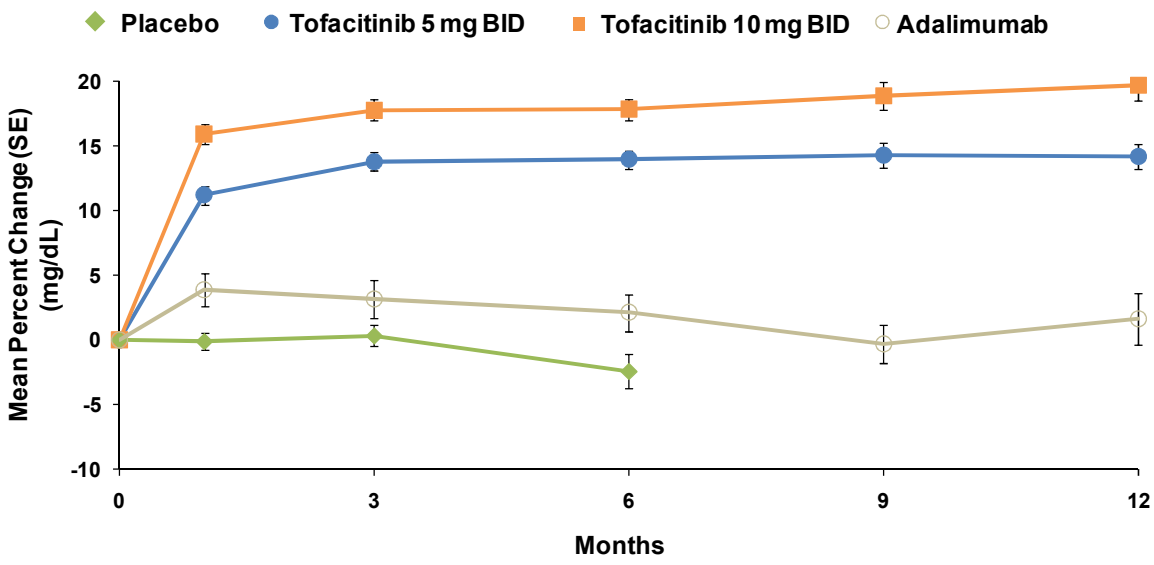
The nearly identical SBP and DBP cumulative frequency distributions seen with tofacitinib, adalimumab and placebo groups, show the lack of difference in blood pressure outliers across these treatment groups, and also the lack of tofacitinib effect on mean changes in BP, thereby indicating that tofacitinib has no clinically meaningful effects on systolic or diastolic blood pressure.

9.7.3.2. Lipid Increases

Dose dependent increases in serum low density lipoprotein cholesterol (LDL-c) (Figure 48), high density lipoprotein cholesterol (HDL-c) (Figure 49) and total cholesterol were observed within 1 to 3 months of the start of tofacitinib therapy, and remained stable thereafter These increases were similar in the monotherapy and background DMARD studies.

In the tofacitinib 10 mg group, the overall increase from pretreatment baseline in LDL-c was approximately 20%, and the increase in HDL-c was approximately 15% to 20%, with little change in the LDL-c/HDL-c ratio. The overall increase in LDL-c and HDL-c were slightly less for the tofacitinib 5 mg group. Data showed little change in the LDL/HDL ratio.

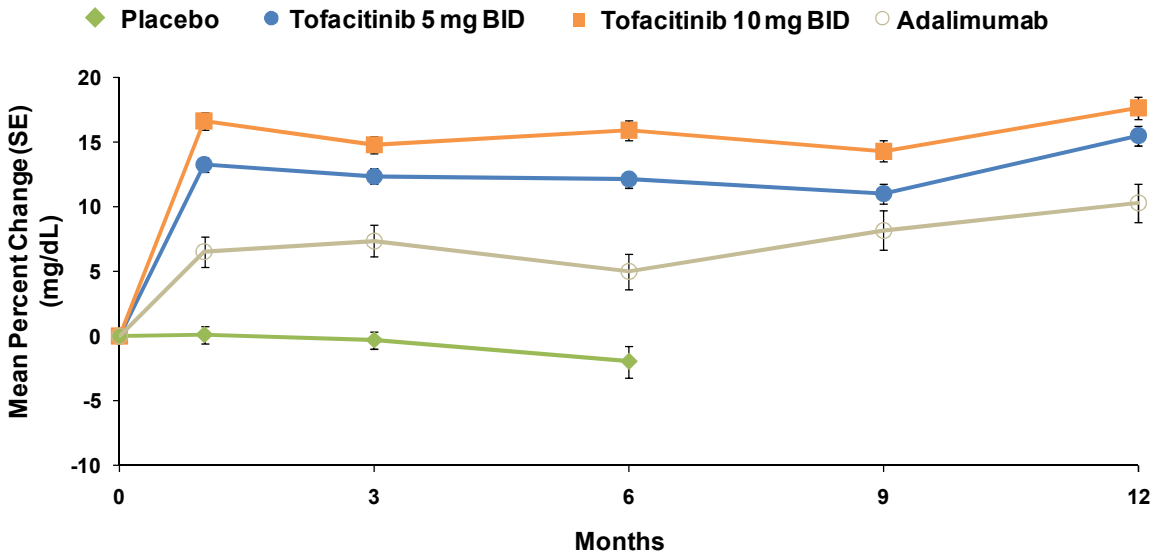
Figure 48. Mean (± SE) Percent Change From Baseline LDL-c (mg/dL) per Visit - All Phase 3 Studies (Overall 0 to 12 Months)



Mean (± SE) Percent Change From Baseline in LDL-c (mg/dL) per Visit - All Phase 3 Studies (Overall 0 to 12 Months)

BID=twice daily; LDL-c=low density lipoprotein cholesterol; SE=standard error

Figure 49. Mean (± SE) Percent Change From Baseline in HDL-c (mg/dL) per Visit in Phase 3 Studies (Overall 0 to 12 Months)



Mean (± SE) Percent Change From Baseline in HDL-c (mg/dL) per Visit in Phase 3 Studies (Overall 0 to 12 Months)

BID=twice daily; HDL-c=high density lipoprotein cholesterol; SE=standard error.

9.7.3.2.1. LDL-c Shift Analyses

Categorical changes in LDL-c as a function of baseline values were analyzed in 2 shift analyses of Phase 3 study data using the following cut-off values recommended in the Adult Treatment Panel III (ATP III) guidelines for the treatment of high blood cholesterol (National Cholesterol Education Program [NCEP] ATP III, 2001): 100, 130, 160, and 190 mg/dL.

The results indicate that there were no marked differences between the 5 and 10 mg doses of tofacitinib in the percentage of patients experiencing an increase in LDL-c values, although this percentage tended to be slightly larger in the 10 mg group. Approximately 40% to 65% of the patients in a baseline category had an increase in LDL-c and moved to a higher ATP III category during the first 3 months of treatment. The percentage of patients was generally higher (approximately 55% to 65%) in the lower baseline LDL-c categories (<100 and 100-130 mg/dL) than in the higher baseline LDL-c categories (40% to 55% in the 130-160 mg/dL and 160-190 mg/dL categories). The analysis of LDL-c changes by baseline LDL-c category and background therapy indicates that there were no differences between the monotherapy and background DMARD studies within each of these categories.

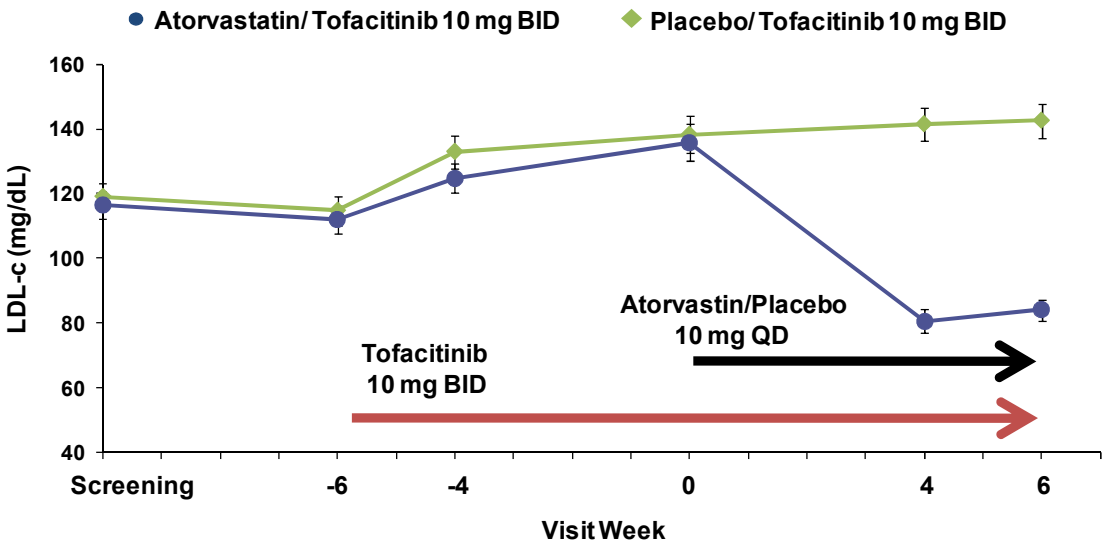
9.7.3.2.2. Study with Atorvastatin in RA Patients Treated with Tofacitinib

Study A3921109 was designed to help characterize the lipid elevations in patients with active RA treated with tofacitinib and to understand the effects of atorvastatin treatment on those lipid changes. Treatment with tofacitinib 10 mg BID during the open-label, 6-week run-in period was associated with changes in lipid parameters similar to those measured in the Phase 2 and 3 RA studies. The key conclusion from this study indicated that the starting

dose of atorvastatin (10 mg daily) was effective at reducing LDL-c and total cholesterol, and to a lesser degree, triglycerides, in patients with active RA treated with tofacitinib 10 mg BID over 6 weeks. As expected, HDL-c was not reduced in response to the addition of atorvastatin treatment.

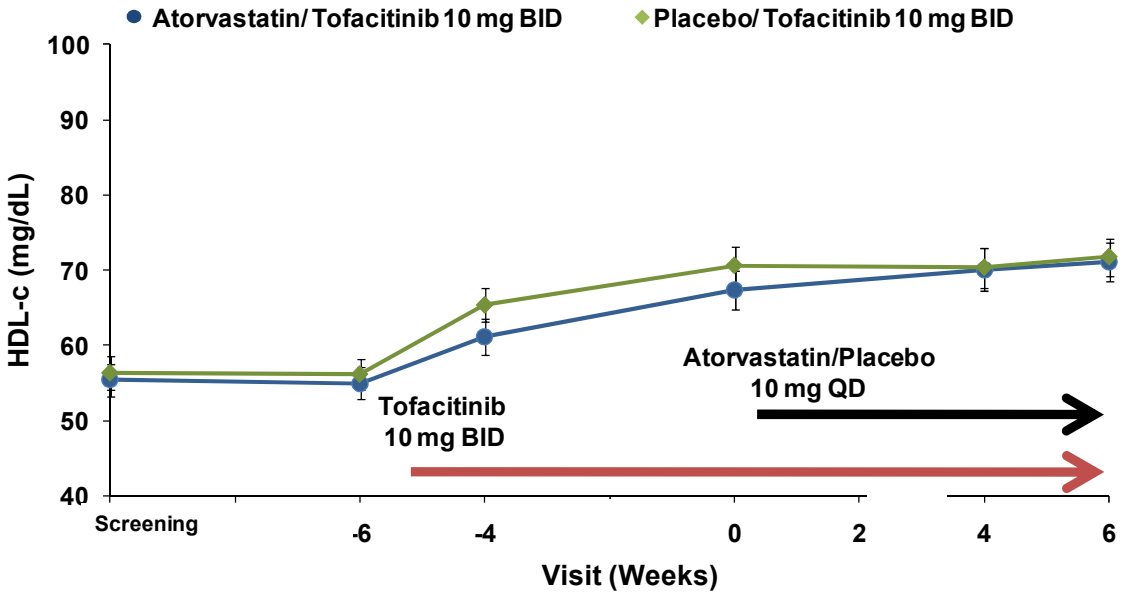
Treatment with atorvastatin 10 mg daily in addition to tofacitinib induced a statistically significant percent reduction in LDL-c from Week 6 compared with placebo plus tofacitinib ($p<0.0001$) (Figure 50). The addition of atorvastatin reduced mean LDL-c below tofacitinib pretreatment means into the optimal target range as specified in the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) cholesterol guidelines. Total cholesterol and apolipoprotein B responded similarly. Serum triglycerides showed modest reduction after initiation of atorvastatin. HDL-c and apolipoprotein A-1 increased with tofacitinib treatment and continued to trend upward, regardless of the treatment group, through the end of the study (Figure 51).

Figure 50. LDL-c Levels in Tofacitinib Treated Patients with Atorvastatin Treatment Compared with Placebo Treated Patients, Study A3921109



BID=twice daily; LDL-c=low density lipoprotein cholesterol; QD=once daily

Figure 51. HDL-c Levels in Tofacitinib Treated Patients with Atorvastatin Treatment Compared with Placebo Treated Patients, Study 1109



BID=twice daily; HDL-c=high density lipoprotein

9.7.3.2.3. Lipid Changes and Cardiovascular Risk

The significance of serum lipid changes in RA patients with respect to cardiovascular risk and the interplay of these changes with inflammation are unknown, as the role of LDL-c levels in the overall cardiovascular risk profile in patients with active RA is currently an active area of investigation. Lipids have been proposed as inverse acute phase reactants known to be affected by inflammatory states and an inverse relationship of lipid levels with RA disease activity has been observed (Bismuth, 2002; Myasoedova, 2011; Choy, 2009). RA patients treated with TNF inhibitors have shown an increase in total cholesterol, HDL-c, LDL-c, triglycerides (TG) and apoprotein (Apo) B levels (Tam, 2007). Also, patients treated with the IL-6 receptor inhibitor tociluzimab have increases in LDL-c, HDL-c, total cholesterol, and triglycerides (Genentech USA, Actemra Prescribing Information).

9.7.3.2.4. Monitoring and Management of Increased Lipids

As proposed in the draft label, assessment of lipid parameters should be performed approximately 4 to 8 weeks following initiation of tofacitinib therapy. Patients should be managed according to local clinical guidelines for the management of hyperlipidemia. Increases in total and LDL cholesterol are reversed with statin therapy.

9.7.3.3. Adjudicated Cardiovascular Events

Adjudication of CV events and deaths was performed by an independent, blinded CV Safety Endpoint Adjudication Committee (CVSEAC) for the Phase 3 studies. CV events to be

adjudicated included death (CV and non-CV) and non-fatal CV events (myocardial infarction, coronary revascularization, CHF, cerebrovascular events, peripheral vascular disease, and hospitalization for unstable angina). Events were assessed using commonly accepted definitions of CV outcomes and pre-specified algorithms to arrive at consistent and objective decisions.

The adjudication process was implemented 25 Feb 2009 after the completion of Phase 2 and before the start of Phase 3, but while LTE studies were still ongoing. Thus adjudicated CV events include only those events that occurred during the entire Phase 3 program but after the implementation date in the LTE studies. Exposures were calculated from either the date of randomization in Phase 3 studies or 25 Feb 2009 in the LTE studies to the date of the event or to the data cutoff date. The use of the implementation date of the adjudication process rather than the date of randomization for determining exposure in the LTE studies underestimated exposures and thus overestimated the actual incidence rates.

Table 46 presents the incidence rate of the adjudicated composite endpoint of major adverse cardiovascular events (MACE), fatal and non-fatal MACE events, and congestive heart failure (CHF) in the tofacitinib-, placebo-, and adalimumab-treated patients in the Phase 3 and LTE studies. The endpoint of MACE was defined as the composite of the following events:

- CV death: coronary, cerebrovascular, cardiac (eg, sudden cardiac death), and non-cardiac vascular (eg, pulmonary embolism)
- Non-fatal CV events: myocardial infarction, cerebrovascular events

The incidence rates of MACE, fatal and non-fatal MACE events, and CHF in the tofacitinib and placebo groups were comparable (Table 46). The incidence rates of adjudicated CV events were consistently lower in the LTE studies than in the Phase 3 studies across all endpoints (Table 46).

The CV event rate in the placebo group and distribution of risk factors at baseline in the Phase 3 population suggest that the patients enrolled in the tofacitinib program had a low CV risk profile. The incidence rates for MACE in the placebo and tofacitinib groups in the Phase 3 population correspond to a 10-year Framingham CV risk of 6% to 10%. This risk is categorized as low in the general population (NCEP ATP III, 2001).

However, it is recognized that RA is associated with accelerated atherosclerosis and an increased CV mortality and morbidity (Van Doornum, 2002; Wolfe, 1994). Numerous studies published over the past decade have further characterized the CV risk in patients with RA and reported an incidence rate for CV events ranging from 1.1 to 5.9 per 100 PYO (Evans, 2011; Jacobsson, 2005; Kremers, 2008; Nicola, 2006; del Rincon, 2001; Solomon, 2006; Watson, 2003). Differences in populations, study methodology, selection, and collection of outcomes and therapeutic interventions for RA likely account for the range of published results. In the Phase 3 tofactinib RA program the rate of MACE was ~50% to 70% lower than in a large population-based study that reported rates of 1.76 and 1.26 events per 100 PYO in men and women with RA, respectively (Watson, 2003). The rates of

cardiovascular events in patients treated with tofacitinib, including ischemic cardiovascular events, congestive heart failure, and cerebrovascular events, are within expected ranges for RA patients. There was no increase in CV event incidence rates as a function of treatment duration, as evidenced by a lower CV event rate in the LTE studies as compared with the Phase 3 studies.

Table 46. Incidence Rates for Adjudicated Cardiovascular Events - Phase 3 Studies and Long-Term Extension Studies

	All Phase 3 Studies (0-12 months)						Long-Term Extension Studies		
		Tofacitinib Treatment					Tofacitinib Treatment		
	Placebo	5 mg BID	10 mg BID	5 + 10 mg BID	All Tofacitinib[c]	Adalimumab	5 mg BID	10 mg BID	All tofacitinib
N	681	1216	1214	2430	3030	204	1370	2145	3515
MACE[a]									
No. of patients	2	4	6	10	12	3	4	5	9
Incidence[b] (95% CI)	0.988 (0.247, 3.952)	0.443 (0.166, 1.180)	0.659 (0.296, 1.467)	0.552 (0.297, 1.025)	0.572 (0.325, 1.008)	1.677 (0.541, 5.198)	0.180 (0.067, 0.478)	0.298 (0.124, 0.715)	0.230 (0.120, 0.443)
Fatal and Non-Fatal MACE									
CV Mortality									
No. of patients	0	0	2	2	2	1	1	0	1
Incidence[b] (95% CI)	0.000	0.000	0.220 (0.055, 0.878)	0.110 (0.028, 0.441)	0.095 (0.024, 0.381)	0.559 (0.079, 3.967)	0.045 (0.006, 0.318)	0.000	0.026 (0.004, 0.181)
Non-fatal Myocardial Infarction									
No. of patients	0	2	2	4	4	2	2	0	2
Incidence[b] (95% CI)	0.000	0.221 (0.055, 0.885)	0.220 (0.055, 0.879)	0.221 (0.083, 0.588)	0.191 (0.072, 0.508)	1.118 (0.280, 4.469)	0.090 (0.022, 0.359)	0.000	0.051 (0.013, 0.205)
Non-fatal Cerebrovascular Accidents									
No. of patients	2	3	2	5	7	0	1	5	6
Incidence[b] (95% CI)	0.988 (0.247, 3.952)	0.332 (0.107, 1.030)	0.220 (0.055, 0.878)	0.276 (0.115, 0.662)	0.334 (0.159, 0.700)	0.000 (0.000, NA)	0.045 (0.006, 0.318)	0.298 (0.124, 0.715)	0.153 (0.069, 0.342)
Congestive Heart Failure									
No. of patients	0	0	5	5	6	0	2	3	5
Incidence[b] (95% CI)	0.000	0.000	0.549 (0.229, 1.320)	0.276 (0.115, 0.662)	0.286 (0.128, 0.637)	0.000	0.090 (0.022, 0.359)	0.178 (0.058, 0.553)	0.128 (0.053, 0.307)

Table 46. Incidence Rates for Adjudicated Cardiovascular Events - Phase 3 Studies and Long-Term Extension Studies

	All Phase 3 Studies (0-12 months)						Long-Term Extension Studies		
		Tofacitinib Treatment					Tofacitinib Treatment		
	Placebo	5 mg BID	10 mg BID	5 + 10 mg BID	All Tofacitinib[c]	Adalimumab	5 mg BID	10 mg BID	All tofacitinib

Phase 3 data as of 29 March 2011; Long term extension study data as of 29 September 2011
BID=twice daily; CI=confidence interval; MACE=major adverse cardiovascular event; N=total patients exposure; q2w=every 2 weeks; SC=subcutaneous.
a. Cardiovascular death, non-fatal myocardial infarction, non fatal cerebrovascular events; A patient who experienced more than one MACE event was counted only once in the MACE category.
b. Incidence (95% CI)=incidence rate per 100 patient-year (95% CI) - crude.
c. Patients in the All Tofacitinib group are those that were initially randomized to placebo and then advanced to tofacitinib treatment at 3 or 6 months
Some events may have occurred after end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.

9.7.3.4. Summary of Cardiovascular Safety

Tofacitinib has no clinically meaningful effects on blood pressure as evidenced by the nearly identical SBP and DBP cumulative frequency distributions seen with tofacitinib, adalimumab and placebo groups, and the lack of tofacitinib effect on mean changes in BP. Dose-dependent increases in LDL-c, HDL-c, and total cholesterol are observed within 1 to 3 months of initiating tofacitinib therapy, and remain stable thereafter. Increases in LDL and total cholesterol are reversed with atorvastatin therapy. Adjudicated review of the cardiovascular events reported in Phase 3 and LTE studies suggests that tofacitinib is not associated with an observed increase in CV events.

9.7.4. Transaminase Elevations and Hepatic Events

Based on a comprehensive evaluation of hepatic safety within the tofacitinib RA program, the potential for hepatic toxicity in patients receiving tofacitinib therapy is low. A summary of the key findings for increased transaminases and possible drug-induced hepatic events in tofacitinib RA program is provided below.

9.7.4.1. Hepatic Laboratory Tests

Increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed with tofacitinib therapy, however increases of ≥3 x the upper limit of normal (ULN) were uncommon in the Phase 3 and LTE studies and also occurred in placebo patients in the Phase 3 studies (Table 47 and Table 48). A dose response was not apparent with tofactinib treatment. Overall, in the LTE studies, the percentage of patients with elevated ALT and AST was greater in the 5 mg tofacitinib group than in the 10 mg group, due to the longer duration of observation in the 5 mg group.

In Phase 3 studies, increases in transaminase levels occurred more frequently in tofacitinib patients on background DMARD therapy (typically MTX) compared with tofacitinib monotherapy patients, although increases ≥3 x ULN were uncommon (Table 47).

Table 47. Transaminase Values* at Multiple of Upper Limit of Normal (Patients With Normal Baseline), in Phase 3 Background DMARD and Monotherapy Studies (0 to 3 Months)

	Tofacitinib			
	5 mg BID N=968	10 mg BID N=962	Placebo N=554	Adalimumab† N=204
Phase 3 Background DMARD Studies				
ALT				
≥1 × ULN	172 (17.77)	204 (21.21)	67 (12.09)	32 (15.69)
≥2 × ULN	18 (1.86)	28 (2.91)	12 (2.17)	0 (0.00)
≥3 × ULN	5 (0.52)	7 (0.73)	0 (0.00)	0 (0.00)
AST				
≥1 × ULN	166 (17.15)	187 (19.44)	54 (9.75)	25 (12.25)
≥2 × ULN	7 (0.72)	12 (1.25)	6 (1.08)	2 (0.98)
≥3 × ULN	3 (0.31)	2 (0.21)	2 (0.36)	0 (0.00)

Table 47. Transaminase Values* at Multiple of Upper Limit of Normal (Patients With Normal Baseline), in Phase 3 Background DMARD and Monotherapy Studies (0 to 3 Months)

	Tofacitinib			
	5 mg BID N=968	10 mg BID N=962	Placebo N=554	Adalimumab† N=204
Phase 3 Monotherapy Study				
ALT				
≥1 × ULN	23 (9.47)	28 (11.43)	11 (9.09)	-
≥2 × ULN	5 (2.06)	5 (2.04)	4 (3.31)	-
≥3 × ULN	1 (0.41)	0 (0.00)	1 (0.83)	-
AST				
≥1 × ULN	23 (9.47)	29 (11.84)	7 (5.79)	-
≥2 × ULN	4 (1.65)	0 (0.00)	1 (0.83)	-
≥3 × ULN	1 (0.41)	0 (0.00)	1 (0.83)	-

Data as of 29 March 2011
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BID=twice daily; DMARD=disease modifying anti-rheumatic drugs; ULN=upper limit of normal.
* Elevations based on the highest values for the time interval
†Monotherapy study does not have adalimumab as a comparator

Table 48. Number (%) of Patients With Liver Test Values at Multiples of Upper Limit of Normal (Patients With Normal Baseline) in Long Term Extension Studies

	Tofacitinib		
	5 mg BID N=1314	10 mg BID N=1869	All Doses N=3183
Total Bilirubin			
≥1 × ULN	108 (8.22)	52 (2.78)	160 (5.03)
≥2 × ULN	2 (0.15)	1 (0.05)	3 (0.09)
≥3 × ULN	2 (0.15)	0 (0.00)	2 (0.06)
AST			
≥1 × ULN	387 (29.45)	440 (23.54)	827 (25.98)
≥2 × ULN	54 (4.11)	35 (1.87)	89 (2.80)
≥3 × ULN	18 (1.37)	12 (0.64)	30 (0.94)
ALT			
≥1 × ULN	377 (28.69)	411 (21.99)	788 (24.76)
≥2 × ULN	80 (6.09)	74 (3.96)	154 (4.84)
≥3 × ULN	24 (1.83)	21 (1.12)	45 (1.41)

Data as of 29 March 2011
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BID=twice daily; ULN=upper limit of normal.
Total patient-years of exposure to tofacitinib: 5 mg BID= 2236.4; 10 mg BID=881.91; All doses= 3118.32

9.7.4.2. Hepatic Disorder Adverse Events

Hepatic disorder adverse events in the Phase 3 and LTE studies were reviewed using the Possible Drug-Related Hepatic Disorder SMQ[1]. Adverse events, serious adverse events, and permanent discontinuations related to possible drug-induced hepatic disorders during the Phase 3 and LTE studies were infrequent (Table 49). Hepatic disorder AEs were reported for 402 patients receiving tofacitinib, of which 12 were SAEs. The most frequently reported hepatic adverse events were increases in liver test values: ALT increased (152), AST increased (120), hepatic enzymes increased (59), gamma-glutamyltransferase increased (48), liver function test abnormal (44), and transaminases increased (36).

In Phase 3 and LTE studies, 53 patients withdrew from the studies due to hepatic disorders, mostly due to increases in transaminases. In Phase 3 studies, 18 tofacitinib treated patients (16 also background MTX) were temporarily discontinued from tofacitinib due to transaminase elevations; none had recurrence of enzyme elevations when tofacitinib was reintroduced. In the LTE studies, 16 tofacitinib treated patients (12 on background MTX) were temporarily discontinued from tofacitinib due to transaminase elevations; only one patient had recurrence of enzyme elevations when tofacitinib was reintroduced. Two patients (one on placebo and one on tofacitinib 5 mg BID) experienced recurrence of transaminase elevations following rechallenge of study drug and were discontinued from the study. Most patients with temporary discontinuations had single episodes of transaminase elevations >2x or >3x ULN and were not associated with increases in bilirubin. In general, hepatic AEs resolved and transaminase elevations reverted back to the patient's baseline or stabilized at <1.5x ULN with continued treatment with tofacitinib.

[1] Adverse events indicative of a hepatic disorder associated with drug therapy are defined as those events that are included in the Standardised MedDRA Query (SMQ) of Possible Drug-Related Hepatic Disorder which is an internationally defined and recognized listing of adverse event terms that relate to this category. MedDRA is an acronym for the Medical Dictionary for Regulatory Activities, which is an international standardized medical terminology used to classify adverse event information associated with the use of biopharmaceuticals and other medical products.

Table 49. Summary of Adverse Events and Exposure-Adjusted Adverse Event Rates in the SMQ of Drug-related Hepatic Disorder in the RA Phase 3 and LTE Studies

Phase 3 Studies (0 to 3 Months)

	Tofacitinib 5 mg BID n (E-AER)	Tofacitinib 10 mg BID n (E-AER)	All Tofacitinib n (E-AER)	Placebo n (E-AER)	Adalimumab 40 mg q2w n (E-AER)
Patients evaluable for AEs	1216	1214	2430	681	204
Total years of exposure	287	288	575	158	47
No. patients with AEs (E-AER)	**30 (10.5)**	**33 (11.5)**	**63 (11.0)**	**15 (9.5)**	**2 (4.3)**
System Organ Class					
Hepatobiliary Disorders	6 (2.09)	7 (2.42)	13 (2.25)	1 (0.63)	0
Investigations (Hepatobiliary lab test findings)	24 (8.36)	26 (9.01)	50 (8.69)	14 (8.87)	2 (4.26)
No. patients with SAEs	0	0	0	1	0
Discontinuations due to AEs	6	3	9	2	0

Phase 3 Studies (3 to 6 Months)

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	All Tofacitinib	Placebo	Adalimumab 40 mg q2w
Patients evaluable for AEs	1451	1439	2890	221	204
Total years of exposure	319	314	634	45	43
No. patients with AEs (E-AER)	**24 (7.5)**	**32 (10.2)**	**56 (8.8)**	**1 (2.2)**	**3 (7.0)**
MedDRA System Organ Class					
Hepatobiliary Disorders	4 (1.25)	2 (0.63)	6 (0.94)	0	0
Investigations (Hepatobiliary lab test findings)	20 (6.26)	30 (9.54)	50 (7.89)	1 (2.22)	3 (6.96)
No.patients with SAEs	1	0	1	0	0
Discontinuations due to AEs	4	5	9	0	1

Phase 3 Studies (> 6 Months)

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Adalimumab 40 mg q2w
Patients evaluable for AEs	1056	1046	2102	204
Total years of exposure	439	437	876	89
No. patients with AEs (E-AER)	**25 (5.7)**	**34 (7.8)**	**59 (6.7)**	**1 (1.1)**
System Organ Class				
Preferred Adverse Event Term				
Hepatobiliary Disorders	2 (0.45)	5 (1.14)	7 (0.79)	0
Investigations (Hepatobiliary lab test findings)	22 (5.00)	29 (6.63)	51 (5.81)	1 (1.12)
Neoplams benign, malignant and unspecified (incl cysts and polyps)	1 (0.22)	0	1 (0.11)	0
Hemangioma of liver	1 (0.22)	0	1 (0.11)	0
No. patients with SAEs	1	0	1	0
Discontinuations due to AEs	1	1	2	0

LTE Studies

	Tofacitinib		
	5 mg BID	**10 mg BID**	**All Doses**
Patients evaluable for AEs	1370	2145	3515
Total years of exposure	2703	1662	4365

No. patients with AEs (E-AER)	**112 (4.1)**	**112 (6.7)**	**224 (5.1)**
System Organ Class			
Preferred Adverse Event Term			
Hepatobiliary disorders	24 (0.88)	27 (1.62)	51 (1.16)
Investigations (Hepatobiliary lab test findings)	92 (3.40)	91 (5.47)	183 (4.19)
Metabolism and nutrition disorders	1 (0.03)	0	1 (0.02)
Neoplams benign, malignant and unspecified (incl cysts and polyps)	1 (0.03)	1 (0.06)	2 (0.04)
Haemangioma of liver	1 (0.03)	0	1 (0.02)
Hepatic neoplasm malignant	0	1 (0.06)*	1 (0.02)
No. patients with SAEs	6	5	11
Discontinuations due to AEs	15	18	33

AEs=adverse events; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BID=twice daily; MedDRA=Medical Dictionary for Regulatory Activities, pt-yr=patient-years; SMQ=standardized MedDRA query; SOC=system organ class
*Patient died

9.7.4.3. Deaths and Other Serious Adverse Events

During the Phase 3 and LTE studies, 12 tofacitinib patients experienced hepatic disorder SAEs. One SAE resulted in death (a patient with malignant hepatic and lung neoplasms) in an LTE study, (within 30 days of last dose of study drug). One patient in the placebo group experienced a hepatic disorder SAE (liver disorder).

Since the 29 March 2011 data cut-off date for the marketing application, a case was reported from a LTE study that describes a 32-year old female patient in Poland who experienced progressively increasing transaminase levels, accompanied by increasing alkaline phosphatase (>2x upper limit of normal, ULN) and subsequent development of hyperbilirubinemia (>2x ULN) accompanied by jaundice. Initial elevations in transaminase levels occurred during treatment with tofacitinib, but a clear worsening of hepatic injury was observed for an additional 2-3 months off study drug with peak abnormalities/severity occurring ~3 months after discontinuation. The event was classified by the investigator as autoimmune hepatitis based on the clinical picture, course of disease, and good response to glucocorticoid and azathioprine treatment. However, the interpretation of the event is confounded by the absence of autoantibodies characteristic of autoimmune hepatitis and absence of typical findings on liver biopsy. Available diagnostic test results did not support a viral etiology. The case is therefore assessed as possible drug induced liver injury (DILI), although there are features, such as the clear worsening of hepatic injury for an additional 2-3 months off drug, which are atypical for DILI. The patient is currently reported to be without symptoms of liver disease, and her hepatic test values have normalized, with the exception of a residual elevation of gamma glutamyl transferase. The patient's prednisone dose has been tapered to 20 mg daily, as of 20 October 2011, and azathioprine 100 mg daily has been continued. Follow-up of her clinical course is ongoing.

Comprehensive assessment of data in tofacitinib-treated RA patients (Phase 1, Phase 2, Phase 3 and LTE studies) indicates that the potential for hepatic toxicity associated with tofacitinib use is low. Elevations in transaminases >3x ULN were seen infrequently (<1%). There were no cases of severe transaminiase elevations that did not have alternate explanations, although in one case DILI could not be definitively ruled out.

9.7.5. Gastrointestinal Perforations

GI perforation has been observed in patients with RA. Gastrointestinal toxicity is a known complication of NSAID use (Wolfe, 2000; Silverstein, 2000; Cannon, 2006; Laine, 2008; Laine, 2007). GI perforations in the tofacitinib RA program were uncommon and primarily involved the lower GI tract. In general, patients who experienced GI perforations in the RA program had other underlying risk factors, including a history of diverticulosis/diverticulitis and/or concomitant drug treatment with NSAIDs and corticosteroids.

To assess the incidence of GI perforations in the tofacitinib RA development program, potential GI perforation events were identified in the patient database. Nineteen cases were identified as potential cases of GI perforation and these cases underwent subsequent clinical review by two Pfizer-employed, board-certified gastroenterologists.

Ten cases were adjudicated as probable (5) or definite (5) GI perforations, yielding an overall incidence rate of 0.144 events per 100 PYO (Table 50). All occurred in the tofacitinib group: 1 on 3 mg (Phase 2); 4 on 5 mg (LTE studies); and 5 on 10 mg (2 in Phase 2, 3 in LTE studies). The GI perforation incidence rate for tofacitinib falls between rates reported for biologic therapies such as TNF inhibitors and the IL-6 inhibitor tocilizumab (van Vollenhoven, 2009-2; Curtis, 2011). The rate of serious GI events (e.g., perforation, obstruction and severe upper gastrointestinal bleeding) range from approximately 0.6 to 4.5 per 100 patient years for upper GI events (Bombardier, 2000) and 0.41 to 0.89 per 100 person years for lower GI events (Laine, 2003).

Table 50. Incidence Rates for Adjudicated GI Perforation in Tofacitinib-Treated Patients in Phase 2, Phase 3, and Long-Term Extension Studies

Definite or Probable	Tofacitinib All Doses
Total no. patients	4791
No. of patients with event	10 (0.2)
Exposure for event (pt-yr)	6921.4
Incidence rate, in events/100 pt-yr (95% CI)	0.144 (0.078, 0.269)

Data as of 29 September 2011
BID=twice daily, pt-yr=patient-years.
Some events may have occurred after the end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.

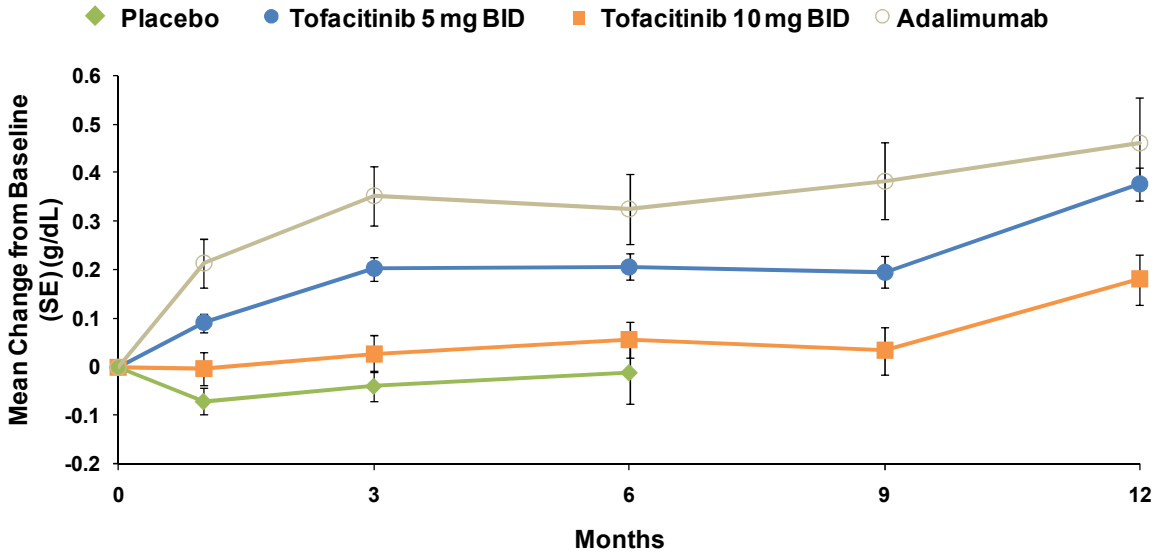
9.7.6. Hemoglobin Levels and Anemia

9.7.6.1. Hemoglobin Levels

Mean hemoglobin levels remained stable or increased from baseline in tofacitinib treated patients in Phase 3 and LTE studies (Figure 52). Patients treated with tofacitinib 5 mg generally showed mean increases in hemoglobin levels from baseline, whereas hemoglobin levels for patients treated with tofacitinib 10 mg remained unchanged from baseline, similar to results for placebo. Hemoglobin levels largely remained within the normal reference range throughout the duration of treatment with tofacitinib. This may be due to improvement in the anemia associated with chronic disease of RA at the 5 mg BID dose, while the

beneficial effects of 10 mg BID dose may be offset by its effect on the hematopoetic system (potentially due to inhibition of erythropoietin signaling through JAK2). Mean hemoglobin levels increased in adalimumab treated patients.

Figure 52. Mean (± SE) Change from Baseline in Hemoglobin (g/dL) in Phase 3 Studies (0 to 12 Months)



BID=twice daily, SE=standard error.

9.7.6.2. Confirmed Anemia

Most cases of confirmed anemia (2 sequential measurements) were mild to moderate in severity, as categorized by modified OMERACT criteria, and occurred with similar frequency in placebo and tofacitinib treated patients in the 0-3 month (placebo controlled) period of the Phase 3 studies (Table 51). Cases of severe anemia were rarely observed.

Most cases of confirmed anemia in the LTE studies were considered to be mild (hemoglogin decrease ≥1 to ≤2 g/dL from baseline) (Table 52). The tofacitinib 5 mg group had more patients with confirmed anemia compared with the 10 mg group, likely due to the longer duration of exposure to study drug.

Table 51. Number (%) of Patients With Confirmed OMERACT Defined* Anemia in Phase 3 Studies (up to 3 Months)

	Tofacitinib				
Hemoglobin Levels	**5 mg BID** N=1220 n (%)	**10 mg BID** N=1217 n (%)	**All Doses** N=2437 n (%)	**Placebo** N=681 n (%)	**Adalimumab** N=204 n (%)
Hgb decrease from baseline ≥1 to ≤2 g/dL	35 (2.9%)	58 (4.8%)	93 (3.8%)	27 (4.0%)	2 (<1.0%)

Table 51. Number (%) of Patients With Confirmed OMERACT Defined* Anemia in Phase 3 Studies (up to 3 Months)

Hemoglobin Levels	Tofacitinib 5 mg BID N=1220 n (%)	Tofacitinib 10 mg BID N=1217 n (%)	Tofacitinib All Doses N=2437 n (%)	Placebo N=681 n (%)	Adalimumab N=204 n (%)
Hgb decrease from baseline >2 to <3 g/dL or absolute value >7 and <8 g/dL	3 (<1.0%)	6 (<1.0%)	9 (<1.0%)	1 (<1.0%)	0
Hgb decrease from baseline ≥3 or absolute value ≤7 g/dL	0	1 (<1.0%)	1 (<1.0%)	1 (<1.0%)	0

BID=twice daily; Hgb=hemoglobin; OMERACT=Outcome Measures in Rheumatoid Arthritis Clinical Trials
*Decreases in hemoglobin were characterized by using the OMERACT criteria in g/dL as follows: mild to moderate = decrease from baseline ≥1 to ≤2 g/dL; severe = decrease from baseline >2 to <3 g/dL or absolute value >7 and <8 g/dL; and potentially life threatening = decrease from baseline ≥3 or absolute value ≤7 g/dL.

Table 52. Number (%) of Patients With Confirmed OMERACT Defined* Anemia in Long Term Extension Studies (All Patients)

Hemoglobin Levels	Tofacitinib 5 mg BID N=1319 n (%)	Tofacitinib 10 mg BID N=1900 n (%)	Tofacitinib All Doses N=3219 n (%)
Hgb decrease from baseline ≥1 to ≤2 g/dL	164 (12.4%)	156 (8.2%)	320 (9.9%)
Hgb decrease from baseline >2 to <3 g/dL or absolute value >7 and <8 g/dL	37 (2.8%)	21 (1.1%)	58 (1.8%)
Hgb decrease from baseline ≥3 or absolute value ≤7 g/dL	17 (1.3%)	6 (<1.0%)	23 (<1.0%)

Data as of 29 March 2011
BID=twice daily, OMERACT=Outcome Measures in Rheumatoid Arthritis Clinical Trials.
*Decreases in hemoglobin were characterized by using the OMERACT criteria in g/dL as follows: mild to moderate = decrease from baseline ≥1 to ≤2; severe = decrease from baseline >2 to <3 or absolute value >7 and <8; and potentially life threatening = decrease from baseline ≥3 or absolute value ≤7.

9.7.6.3. Monitoring and Management of Anemia

As proposed in the draft label, hemoglobin should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter. Overall, the risk of clinically important anemia is manageable with appropriate patient screening and monitoring. It is not recommended to initiate tofacitinib treatment in patients with a low hemoglobin level, i.e. < 9 g/dL. Treatment with tofacitinib should be interrupted in patients who develop hemoglobin levels < 8 g/dL or whose hemoglobin level drops greater than ≥2 g/dL on treatment.

Patients with new onset anemia should undergo the appropriate evaluation for the cause of the anemia.

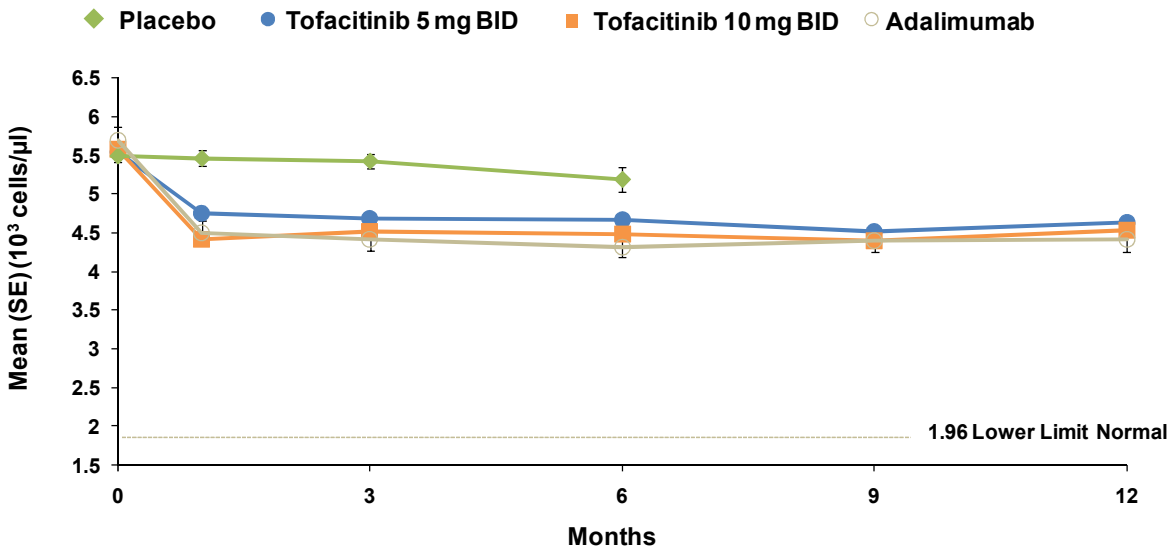
9.7.7. Absolute Neutrophil Counts and Neutropenia

9.7.7.1. Absolute Neutrophil Counts

A dose dependent mean decrease in absolute neutrophil counts, which reached a plateau within 3 months of treatment, was observed in RA patients treated with tofacitinib (Figure 53). Neutrophil counts largely remained within the normal reference range throughout the duration of treatment with tofacitinib. These data are consistent with exposure-response modeling of Phase 2 data predicting a steady state neutrophil nadir by 6 to 8 weeks and a median decrease from baseline of 1.0 and 1.5 x 10^3/L) for tofacitinib 5 mg and 10 mg, respectively. After cessation of tofacitinib administration, neutrophil counts recovered in a dose dependent manner by 6 weeks.

Modest decreases in neutrophils are expected with efficacious RA treatment. Mean decreases in neutrophil counts of a similar magnitude as those with tofacitinib treatment groups were also observed in the adalimumab treated patients, with corresponding reductions in acute phase reactants. This suggests that changes in neutrophils may be primarily related to decreasing inflammation, and are not specific to the mechanism of action of tofacitinib.

Figure 53. Mean (SE) Neutrophil Levels in Phase 3 Studies (0 to 12 Months)



BID=twice daily; SE=standard error.

9.7.7.2. Confirmed Neutropenia

Neutropenia occurs among RA patients undergoing treatment with DMARDs, including TNF inhibitors (Hastings, 2010; Rajakulendran, 2006) and tocilizumab (Genentech, 2011). It has been reported that 14.3% to 23.1% of RA patients treated with TNF inhibitors developed neutropenia (Rajakulendran, 2006; Hastings, 2010).

No cases of confirmed (two sequential) neutrophil counts of <500 cells/mm^3 have been observed in the controlled Phase 3 and LTE studies. In general, less than 1.0% of tofacitinib treated patients had confirmed neutropenia with ANC <1.5 to ≥ 0.5 cells/ mm^3 in the Phase 3 and LTE studies (Table 53 and Table 54). This frequency of confirmed neutropenia in tofacitinib treated patients is similar or below that reported for RA patients receiving therapy with TNF inhibitors, MTX and other nonbiologic DMARDs, and NSAIDs (Kalksma, 2002).

Table 53. Number (%) of Patients With Confirmed OMERACT Defined Neutropenia in Phase 3 Studies (0 to 3 Months)

	Tofacitinib				
Absolute Neutrophil Counts	**5 mg BID** N=1220 n (%)	**10 mg BID** N=1217 n (%)	**All Doses** N=2437 n (%)	**Placebo** N=681 n (%)	**Adalimumab** N=204 n (%)
≥1.5 to <2 ANC×1000/mm^3	18 (1.5%)	24 (2.0%)	42 (1.7)	7 (<1.0%)	2 (<1.0%)
<1.5 to ≥ 0.5 ANC×1000/mm^3	2 (<1.0%)	7 (<1.0%)	9 (<1.0%)	2 (<1.0%)	1 (<1.0%)
<0.5 ANC×1000/mm^3	0	0	0	0	0

ANC=absolute neutrophil count , BID=twice daily; OMERACT=Outcome Measures in Rheumatoid Arthritis Clinical Trials
Neutropenia defined by OMERACT criteria in ANC×1000/mm^3 as mild, ≥1.5 to <2; moderate to severe, <1.5 to ≥ 0.5; and potentially life threatening, <0.5

Table 54. Number (%) of Patients With Confirmed OMERACT Defined Neutropenia in Long Term Extension Studies

Absolute Neutrophil Counts	**Tofacitinib 5 mg BID** N=1319 n (%)	**Tofacitinib 10 mg BID** N=1900 n (%)	**Tofacitinib All Doses** N=3219 n (%)
≥1.5 to <2 ANC×1000/mm^3	55 (4.2%)	37 (1.9%)	92 (2.9%)
<1.5 to ≥ 0.5 ANC×1000/mm^3	8 (<1.0%)	8 (<1.0%)	16 (<1.0%)
<0.5 ANC×1000/mm^3	0	0	0

Data as of 29 March 2011
ANC=absolute neutrophil count, BID=twice daily; OMERACT=Outcome Measures in Rheumatoid Arthritis Clinical Trials
Neutropenia defined by OMERACT criteria in ANC×1000/mm^3 as mild, ≥1.5 to <2; moderate to severe, <1.5 to ≥ 0.5; and potentially life threatening, <0.5
Total patient-years of exposure to tofacitinib: 5 mg BID= 2236.41; 10 mg BID=881.91; All doses=3118.32

9.7.7.3. Neutropenia and Serious Infection

To ascertain whether the development of neutropenia was associated with a heightened risk for infection, patients were divided into those who did and did not develop neutropenia (ANC <2000) and then according to whether they developed a treated infection or a serious infection (defined as one that required either hospitalization or parenteral antimicrobial therapy). Since neutropenia may increase the risk of infection at a time proximate to the

neutropenic event, the percentage of treated or serious infections that occurred in the 30 days following the confirmed neutropenic episode was compared to the percentage of these infections observed in the 30 days following the lowest neutrophil count among patients who did not experience confirmed neutropenia.

There was no identified association between the occurrence of treated or serious infections and low neutrophil counts in tofacitinib treated patients in the Phase 3 and LTE studies. Table 55 and Table 56 present the number of patients with confirmed neutropenia in the presence of serious infection. No relationship was observed between neutropenia of any level and the development of treated or serious infections. Also, no relationship was seen between confirmed neutropenia and serious and treated infection that occurred in the 30 days following the confirmed neutropenic episode.

Table 55. Number (%) of Patients With Confirmed Neutropenia by Presence of Serious Infection in All Phase 3 Studies (Overall 0 to 12 Months)

Confirmed Neutropenia	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		Pbo → Tofacitinib 5 mg BID		Pbo → Tofacitinib 10 mg BID		Adali 40 mg SC q2w	
	N	n [a](%)	N	n [a](%)	N	n [a](%)	N	n [a](%)	N	n [a](%)
None	1187	28 (2.4)	1165	27 (2.3)	333	4 (1.2)	326	4 (1.2)	197	3 (1.5)
≥1.5 to <2 ANC×1000/mm^3	29	1 (3.4)	33	0 (0.0)	8	0 (0.0)	9	0 (0.0)	5	0 (0.0)
<1.5 to ≥ 0.5 ANC×1000/mm^3	4	0 (0.0)	19	0 (0.0)	2	0 (0.0)	3	0 (0.0)	2	0 (0.0)
<0.5 ANC×1000/mm^3	0	0	0	0	0	0	0	0	0	0
Total patients	1220	29 (2.4)	1217	27 (2.2)	343	4 (1.2)	338	4 (1.2)	204	3 (1.5)

Data as of 29 March 2011
Adali=adalimumab, ANC=absolute neutrophil count , BID=twice daily, OMERACT=Outcome Measures in Rheumatoid Arthritis Clinical Trials, q2w= every 2 weeks, SC=subcutaneous.
[a] Number of patients with treated infections
Neutropenia defined by OMERACT criteria in ANC×1000/mm^3 as mild, ≥1.5 to <2; moderate to severe, <1.5 to ≥ 0.5; and potentially life threatening, <0.5

Table 56. Number (%) of Patients With Confirmed Neutropenia by Presence of Serious Infection in Long-Term Extension Studies

Confirmed Neutropenia	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		Tofacitinib All Doses	
	N	n [a](%)	N	n [a](%)	N	n [a](%)
None	1256	49 (3.9)	1855	42 (2.3)	3111	91 (2.9)
≥1.5 to <2 ANC×1000/mm^3	55	0 (0.0)	37	1 (2.7)	92	1 (1.1)
<1.5 to ≥ 0.5 ANC×1000/mm^3	8	1 (12.5)	8	0 (0.0)	16	1 (6.3)
<0.5 ANC×1000/mm^3	0	0	0	0	0	0
Total patients	1319	50 (3.8)	1900	43 (2.3)	3219	93 (2.9)

Data as of 29 March 2011
ANC=absolute neutrophil count, BID=twice daily, OMERACT=Outcome Measures in Rheumatoid Arthritis Clinical Trials.
[a] Number of patients with treated infections
Neutropenia defined by OMERACT criteria in ANC×1000/mm^3 as mild, ≥1.5 to <2; moderate to severe, <1.5 to ≥ 0.5; and potentially life threatening, <0.5
Total patient-years of exposure to tofacitinib: 5 mg BID=2236.41; 10 mg BID=881.91; All doses=3118.32.

9.7.7.4. Monitoring and Management of Decreased Neutrophils/Neutropenia

As proposed in the draft label, it is not recommended to initiate tofacitinib treatment in patients with a low neutrophil count, i.e., ANC <1000/mm^3. For patients who develop a persistent ANC between 500 to 1000/mm^3, reduce tofacitinib dose or interrupt dosing until ANC > greater than 1000/mm^3. In patients who develop an ANC <500/mm^3 treatment is not recommended. Neutrophils should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter.

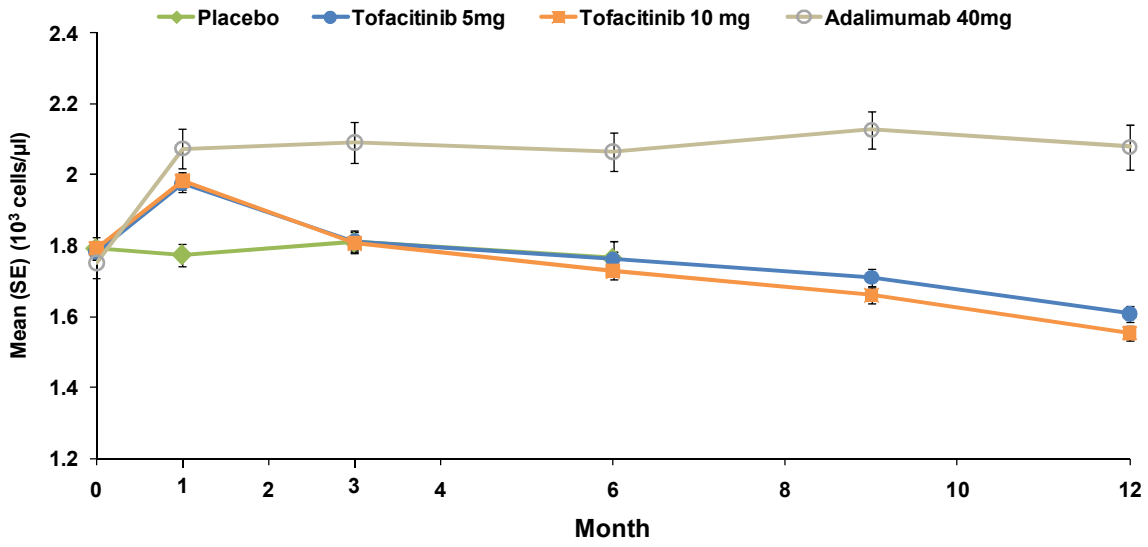
9.7.8. Absolute Lymphocyte Counts and Lymphopenia

9.7.8.1. Absolute Lymphocyte Counts

In the Phase 3 studies, mean increases from baseline in peripheral blood absolute lymphocyte counts were seen in the 5 and 10 mg tofacitinib groups, and the adalimumab group at Month 1. These increases persisted for adalimumab, but not for the tofacitinib groups, through Month 12 (Figure 54).

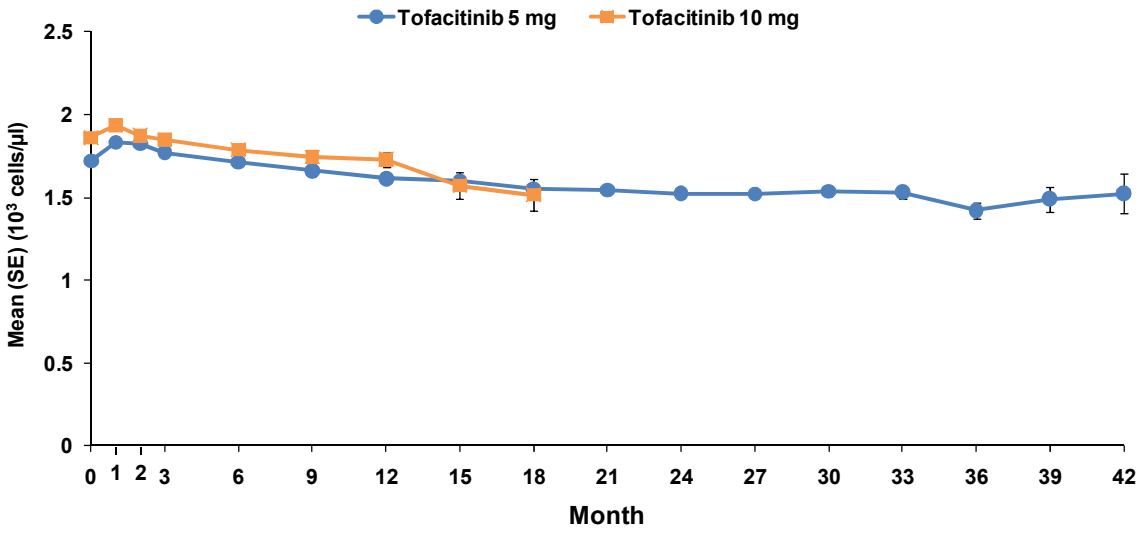
In the LTE studies, small, variable mean changes from baseline were seen in both tofacitinib groups, with no differences between the tofacitinib doses. These levels generally remained stable for the duration of treatment (Figure 55).

Figure 54. Mean (SE) Lymphocyte Levels in Phase 3 Studies (0 to 12 Months)



SE=standard error

Figure 55. Mean (SE) Lymphocyte Levels in Long Term Extension Studies



SE=standard error

9.7.8.2. Confirmed Lymphopenia

Phase 3 Studies

No patients in the tofacitinib 5 mg group and < 1% in the 10 mg group had OMERACT-defined confirmed lymphopenia of <500 cells/µL in the placebo-controlled portion of the Phase 3 studies (Table 57 and Table 58). Both tofacitinib dose groups and placebo had a similar number of confirmed cases of lymphopenia in the Phase 3 studies. Fewer tofacitinib patients in the Phase 3 monotherapy study had confirmed lymphopenia in the <1.5 to ≥0.5 x1000 cells/µL range (<17%) compared with the background DMARD studies (<25%). Less lymphopenia was observed in the adalimumab group likely driven by the mean increase in lymphocytes typically seen in patients receiving adalimumab treatment.

Table 57. Number (%) of Patients With Confirmed Lymphopenia in Phase 3 Background DMARD Studies, 0-3 months

Lymphocyte Counts	Tofacitinib 5 mg BID N=976 n (%)	Tofacitinib 10 mg BID N=972 n (%)	Tofacitinib All Doses N=1948 n (%)	Placebo N=559 n (%)	Adalimumab N=204 n (%)
≥1.5 to <2 Lymphocytes ×1000/mm³	227 (23.3)	241 (24.8)	468 (24.0)	127 (22.7)	41 (20.1)
<1.5 to ≥ 0.5 Lymphocytes ×1000/mm³	240 (24.6)	218 (22.4)	458 (23.5)	174 (31.1)	25 (12.3)
<0.5 Lymphocytes ×1000/mm³	0	1 (<1.0)	1 (<1.0)	0	0

Data as of 29 March 2011
BID=twice daily; OMERACT=Outcome Measures in Rheumatoid Arthritis Clinical Trials.
Lymphopenia defined by OMERACT criteria in counts lymphocytes ×1000/mm³ as mild, ≥1.5 to <2; moderate to severe, <1.5 to ≥ 0.5; and potentially life threatening, <0.5.
Total patient-years of exposure to Tofacitinib:5 mg BID=2236.41; 10 mg BID=881.91; All doses=3118.32

Table 58. Number (%) of Patients With Confirmed Lymphopenia in Phase 3 Tofacitinib Monotherapy Study, 0-3 months

Lymphocyte Counts	Tofacitinib 5 mg BID N=244 n (%)	Tofacitinib 10 mg BID N=245 n (%)	Tofacitinib All Doses N=489 n (%)	Placebo N=122 n (%)
≥1.5 to <2 Lymphocytes ×1000/mm^3	60 (24.6)	56 (22.9)	116 (23.7)	29 (23.8)
<1.5 to ≥ 0.5 Lymphocytes ×1000/mm^3	41 (16.8)	37 (15.1)	78 (16.0)	21 (17.2)
<0.5 Lymphocytes ×1000/mm^3	0	0	0	0

Data as of 29 March 2011
BID=twice daily; OMERACT=Outcome Measures in Rheumatoid Arthritis Clinical Trials.
Lymphopenia defined by OMERACT criteria in counts lymphocytes ×1000/mm^3 as mild, ≥1.5 to <2; moderate to severe, <1.5 to ≥ 0.5; and potentially life threatening, <0.5.
Total patient-years of exposure to tofacitinib:5 mg BID=2236.41; 10 mg BID=881.91; All doses=3118.32

LTE Studies

Number of patients with confirmed lymphopenia in the LTE studies is presented in Table 59 and Table 60. Less than 1% of patients in either the tofacitinib 5 or 10 mg group had OMERACT-defined confirmed lymphopenia of <500 cells/µL in the LTE studies. The number of cases of confirmed lymphopenia at levels between ≥ 1.5 to <2 x1000 cells/µL, were similar (<29%) in each of the tofacitinib groups. The tofacitinib 5 mg group had a higher percentage (~60%) of lymphopenia at levels between <1.5 to ≥0.5 x1000 cells/µL compared with the 10 mg group (~32%), which was likely because of the greater duration of observation in the tofacitinib 5 mg group.

Table 59. Number (%) of Patients With Confirmed Lymphopenia in Long Term Extension Studies, on Tofacitinib with Background DMARD

Lymphocyte Levels	Tofacitinib 5 mg BID N=732 n (%)	Tofacitinib 10 mg BID N=1285 n (%)	Tofacitinib All Doses N=2017 n (%)
≥1.5 to <2 Lymphocytes ×1000/mm^3	163 (22.3)	311 (24.2)	474 (23.5)
<1.5 to ≥ 0.5 Lymphocytes ×1000/mm^3	441 (60.2)	393 (30.6)	834 (41.3)
<0.5 Lymphocytes ×1000/mm^3	5 (<1.0)	2 (<1.0)	7 (<1.0)

Data as of 29 March 2011
BID=twice daily; N=number of patients; OMERACT=Outcome Measures in Rheumatoid Arthritis Clinical Trials.
Lymphopenia defined by OMERACT criteria in counts lymphocytes ×1000/mm^3 as mild, ≥1.5 to <2; moderate to severe, <1.5 to ≥ 0.5; and potentially life threatening, <0.5.
Total patient-years of exposure to tofacitinib: 5 mg BID=2236.41; 10 mg BID=881.91; All doses=3118.32

Table 60. Number (%) of Patients With Confirmed Lymphopenia in Long Term Extension Studies, on Tofacitinib Monotherapy

Lymphocyte Levels	Tofacitinib 5 mg BID N=587 n (%)	Tofacitinib 10 mg BID N=615 n (%)	Tofacitinib All Doses N=1202 n (%)
≥1.5 to <2 Lymphocytes ×1000/mm^3	155 (26.4)	175 (28.5)	330 (27.5)
<1.5 to ≥ 0.5 Lymphocytes ×1000/mm^3	332 (56.6)	198 (32.2)	530 (44.1)
<0.5 Lymphocytes ×1000/mm^3	1 (<1.0)	2 (<1.0)	3 (<1.0)

Data as of 29 March 2011
BID=twice daily;
Lymphopenia defined by OMERACT criteria in counts lymphocytes ×1000/mm^3 as mild, ≥1.5 to <2; moderate to severe, <1.5 to ≥ 0.5; and potentially life threatening, <0.5.
Total patient-years of exposure to tofacitinib: 5 mg BID=2236.41; 10 mg BID=881.91; All doses=3118.32

9.7.8.3. Lymphopenia and Serious Infection

The number and percentage of patients with serious infections are shown by treatment group in patients with confirmed lymphopenia in the Phase 3 background DMARD studies (Table 61), Phase 3 Monotherapy studies (Table 62), and the LTE studies (Table 63).

There was no observable association between confirmed lymphopenia with lymphocyte levels ≥500 cells/μL to <2000 cells/μL and the occurrence of serious infections; occurrence of serious infections in this lymphocyte range is similar amongst tofacitinib treatment groups and placebo in Phase 3 studies. In patients with a confirmed lymphocyte count below 500 cells/μL at any time during the course of treatment in the LTE studies, the proportion of patients with a serious infection was increased with tofacitinib patients, although numbers are small.

Table 61. Number (%) of Patients With Confirmed Lymphopenia by Presence of Serious Infection in Phase 3 Studies, Tofacitinib with Background DMARD Studies, 0-12 Months

	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		Tofacitinib All Doses		Placebo		Adalimumab	
Confirmed Lymphopenia	N	n *(%)	N	n *(%)	N	n *(%)	N	n *(%)	N	n *(%)

Table 61. Number (%) of Patients With Confirmed Lymphopenia by Presence of Serious Infection in Phase 3 Studies, Tofacitinib with Background DMARD Studies, 0-12 Months

	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		Tofacitinib All Doses		Placebo		Adalimumab	
None	299	17 (5.7)	286	10 (3.5)	585	27 (4.6)	177	1 (0.6)	97	3 (3.1)
≥1.5 to <2 Lymphocytes×1000/mm^3	274	5 (1.8)	280	6 (2.1)	554	11 (2.0)	154	2 (1.3)	64	0
<1.5 to ≥ 0.5 Lymphocytes ×1000/mm^3	403	6 (1.5)	401	7 (1.7)	804	13 (1.6)	228	4 (1.8)	43	0
<0.5 Lymphocytes ×1000/mm^3	0	0	5	0	5	0	0	0	0	0
Total	976	28 (2.9)	972	23 (2.4)	1948	51 (2.6)	559	7 (1.3)	204	3 (1.5)

Data as of 29 March 2011
BID=twice daily, OMERACT=Outcome Measures in Rheumatoid Arthritis Clinical Trials.
* Number of patients with serious infections.
Lymphopenia defined by OMERACT criteria in counts lymphocytes ×1000/mm^3 as mild, ≥1.5 to <2; moderate to severe, <1.5 to ≥ 0.5; and potentially life threatening, <0.5.

Table 62. Number (%) of Patients With Confirmed Lymphopenia by Presence of Serious Infection in Phase 3 Studies, Tofacitinib Monotherapy, 0-6 Months

	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		Placebo → 5 mg Tofacitinib BID		Placebo → 10 mg Tofacitinib BID	
Confirmed Lymphopenia	**N**	**n *(%)**	**N**	**n *(%)**	**N**	**n *(%)**	**N**	**n *(%)**
None	103	0	118	1 (0.8)	31	1 (3.2)	26	0
≥1.5 to <2 Lymphocytes×1000/mm^3	82	1 (1.2)	67	1 (1.5)	16	0	17	0
<1.5 to ≥ 0.5 Lymphocytes ×1000/mm^3	59	0	60	2 (3.3)	14	0	18	0
<0.5 Lymphocytes ×1000/mm^3	0	0	0	0	0	0	0	0
Total	244	1 (0.4)	245	4 (1.6)	61	1 (1.6)	61	0

Data as of 29 March 2011
BID=twice daily, OMERACT=Outcome Measures in Rheumatoid Arthritis Clinical Trials.
* Number of patients with serious infections.
Lymphopenia defined by OMERACT criteria in counts lymphocytes ×1000/mm^3 as mild, ≥1.5 to <2; moderate to severe, <1.5 to ≥ 0.5; and potentially life threatening, <0.5.

Table 63. Number (%) of Patients With Confirmed Lymphopenia by Presence of Serious Infection in Long-Term Extension Studies

Confirmed Lymphopenia	Tofacitinib 5 mg BID N	Tofacitinib 5 mg BID n* (%)	Tofacitinib 10 mg BID N	Tofacitinib 10 mg BID n* (%)	Tofacitinib All Doses N	Tofacitinib All Doses n* (%)
None	222	8 (3.6)	819	19 (2.3)	1041	27 (2.6)
≥1.5 to <2 Lymphocytes×1000/mm^3	318	10 (3.1)	486	9 (1.9)	804	19 (2.4)
<1.5 to ≥ 0.5 Lymphocytes ×1000/mm^3	773	30 (3.9)	591	13 (2.2)	1364	43 (3.2)
<0.5 Lymphocytes ×1000/mm^3	6	2 (33.3)	4	2 (50.0)	10	4 (40.0)
Total	1319	50 (3.8)	1900	43 (2.3)	3219	93 (2.9)

Data as of 29 March 2011
BID=twice daily, OMERACT=Outcome Measures in Rheumatoid Arthritis Clinical Trials.
* Number of patients with serious infections.
Lymphopenia defined by OMERACT criteria in counts×1000/mm^3 as mild, ≥1.5 to <2; moderate to severe, <1.5 to ≥ 0.5; and potentially life threatening, <0.5.
Total patient-years of exposure to tofacitinib:5 mg BID=2236.41; 10 mg BID=881.91; All doses=3118.32

9.7.8.4. Exposure-Response Relationship for Lymphocyte Subpopulations

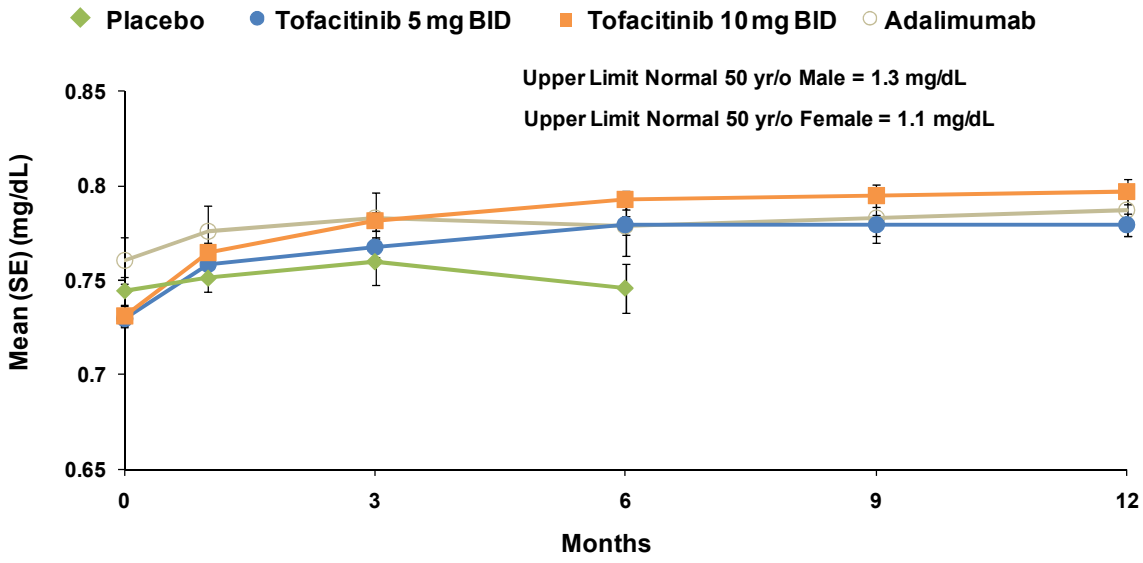
Because of the key roles played by JAK1 and JAK3 in lymphocyte cell development and homeostasis, the effects of tofacitinib treatment on changes in numbers of CD3+ cells (pan T-lymphocytes), CD4+ cells (helper T cells), CD8+ cells (cytotoxic T cells), CD19+ cells (B cells) and CD16/+CD56+ cells (natural killer [NK] cells) were assessed in 3 Phase 2 studies with the overall purpose of evaluating their predictive value for adverse events such as infections and malignancy. Visual assessment of dose-response plots indicated that changes in CD3+, CD4+, and CD8+ counts were variable and did not show a consistent pattern of dose response across studies. In contrast, NK cell counts showed dose-dependent decreases, and B-cell counts showed dose-dependent increases in all 3 studies. The physiologic implications of an increase in circulating B cell numbers in response to JAK inhibition are unclear, since JAK3 -/- humans have increased numbers of circulating B cells accompanied by severe reductions in serum immunoglobulin levels. The modest decreases in serum IgG, IgM, and IgA levels observed in tofacitinib-treated RA patients in one Phase 2 study may be due to changes in RA disease activity. Model-based characterization of NK cell counts indicated that reductions in NK cell counts were predicted to reach nadir (steady-state) by 8 to 10 weeks after initiation of tofacitinib treatment, with approximately 36% and 47% peak mean reductions for the 5 mg and 10 mg doses, respectively. Consistent with follow-up data from Phase 2 Study 1019, NK cells counts are predicted to return to within 10% of baseline, on average, within 2 to 6 weeks after cessation of therapy for both the 5 and 10 mg doses of tofacitinib. Logistic regression of NK cells counts versus incidence of serious infections, herpes zoster or malignancy did not show an association between lower NK cell counts and increased incidence of serious infections or malignancies.

9.7.9. Serum Creatinine and Renal Events

9.7.9.1. Serum Creatinine Levels

Mean serum creatinine levels increased from baseline in all treatment groups, including placebo and adalimumab, in the Phase 3 studies. Increases in mean serum creatinine levels in tofacitinib treated patients were estimated to be 0.02 and 0.04 mg/dl greater than placebo in patients treated with the 5 mg and 10 mg tofacitinib doses, respectively, at Month 3. Increases reached a plateau within 3 months of initiation of therapy, and remained stable thereafter (Figure 56). In the LTE studies there was no progressive increase in mean changes in creatinine from Phase 3 levels (Appendix Figure 65). The percentage of patients requiring discontinuation due to elevated creatinine (2 consecutive increases >50% from the average of screening and baseline) in the Phase 3 studies was low (<1%).

Figure 56. Mean (SE) Serum Creatinine Levels in Phase 3 Studies (0 to 12 Months)



SE=standard error

Reversibility of Creatinine Levels

Reversibility of serum creatinine levels was assessed in an early Phase 2 study in which tofacitinib was administered to RA patients for 6 weeks, followed by a 6 week washout period. Mean increases from baseline of up to 0.04 mg/dl observed with the 5 mg BID dose during the 6-week treatment period returned to ≤0.01 mg/dl of the pre-treatment baseline within 2-6 weeks, indicating that increases in creatinine are reversible.

Creatinine Level Shift Analysis

To further examine the serum creatinine changes, patients were categorized into 4 cohorts based on the percent change in creatinine from baseline to the end of treatment (EoT) in the Phase 3 studies and to the last observed visit (LoV) in the ongoing LTE studies (Table 64).

Mean changes in creatinine from baseline to the EoT in the Phase 3 and to LoV in the LTE studies were then calculated for each of these cohorts to assess whether patients with larger increases in creatinine in the Phase 3 studies showed the same or greater mean changes in creatinine values in the LTE studies. Patients who exhibited a greater than 10% increase in creatinine at the EoT in Phase 3 had very similar mean changes at both EoT in Phase 3 and at the LoV in the LTE studies (Table 64). These data indicate that patients with larger changes in creatinine in the Phase 3 studies did not demonstrate a further increase in creatinine levels in the LTE studies. Individual patient creatinine levels largely remained within reference range.

Table 64. Mean Changes in Creatinine From Baseline, Phase 3 and LTE Studies

Patient Categories of Creatinine Increase at EoT in Phase 3	Mean Increase at EoT in Phase 3 Studies mg/dL (%)	Mean Increase at LoV in LTE Studies mg/dL (%)
≤10%	0.00 (0.3)	0.05 (7.5)
>10 to <33%	0.13 (18.6)	0.13 (18.5)
≥33 to ≤50%	0.25 (38.2)	0.24 (36.5)
>50%	0.32 (56.0)	0.26 (44.9)

EoT=end of treatment, LoV=last observed visit, LTE=long-term extension

9.7.9.2. Potential Mechanisms for Creatinine Increases

The exact mechanism for the changes in serum creatinine is not known, however a number of plausible mechanisms have been investigated and are discussed below.

The results of these investigations show that no changes were seen in measured glomerular filtration rate (GFR), effective renal plasma flow (ERPF), creatinine clearance, (Section 9.7.9.2.1), or secretion of creatinine in healthy volunteers who were administered tofacitinib (Section 9.7.9.2.2).

Multivariate analyses were conducted to understand if there are other factors that may be associated with the small increases in creatinine (Section 9.7.9.2.3).

Investigations into possible mechanisms of creatinine increases is ongoing with a measured GFR study currently being conducted in RA patients treated with tofactinib.

9.7.9.2.1. Phase 1 Study to Evaluate Potential Effect of Tofacitinib on Renal Function

A Phase 1 study was conducted to evaluate the effect of tofacitinib on renal function, effective renal plasma flow and creatinine clearance in healthy volunteers. Volunteers were randomized in a 2:1 ratio to receive either tofacitinib 15 mg BID or placebo BID for 14 days. The effect of tofacitinib on GFR was measured by iohexol serum clearance, ERPF by para-aminohippuric acid (PAH) urinary clearance, and creatinine clearance by 24-hour urine collection on Day 1 (predose) and Day 15. No changes were seen in measured GFR, ERPF, and creatinine clearance in the tofacitinib group compared with the placebo group.

9.7.9.2.2. Phase 1 Study to Evaluate Potential Effect of Tofacitinib on Renal Tubular Secretion

A Phase 1 study evaluated the potential effect of tofacitinib on the PK of metformin (a probe drug for renal organic cation transport [OCT]). Metformin was used in this study as a more sensitive marker than creatinine of OCT inhibition. The study showed that co-administration of multiple-doses of tofacitinib with metformin resulted in no difference in the PK of metformin. Thus, there is no evidence of an effect of tofacitinib on renal organic cation transport and, by extension, no effect of tofacitinib on renal tubular secretion of creatinine in healthy volunteers.

9.7.9.2.3. CRP Levels and Changes in Creatinine

Multivariate analyses have revealed an association between baseline CRP and creatinine ($p<0.05$). Patients with higher baseline CRP had lower creatinine at baseline and showed a larger absolute and fractional dose-dependent increase in creatinine upon treatment with tofacitinib compared to those with lower baseline CRP. The results suggest that pretreatment inflammatory burden in RA patients may help explain the observed changes in creatinine.

9.7.9.3. Renal Failure Adverse Events

A clinical review was performed on patients in the Phase 3 and LTE studies with events of possible acute renal failure, based on AEs listed in the SMQ of Acute Renal Failure, as of 29 March 2011. Profiles and/or narratives of 43 identified patients were reviewed to ascertain potential etiologies for the event. Data reviewed included demographics, adverse event(s), day of onset, day of resolution or last evaluation, serum creatinine, creatinine clearance calculated by Cockcroft-Gault, value for maximum serum creatinine achieved, tofacitinib dose, concomitant medications, past medical history, associated or concurrent events, action taken (permanently discontinued, temporarily discontinued, dose reduced, or none), outcome of the event (resolution, improvement, persistence, worsening, or patient died), investigator and Pfizer case assessments.

Of the 43 patients included in the review, 19 were receiving tofacitinib 5 mg at the time of the event, 22 were receiving tofacitinib 10 mg, and 2 were receiving placebo. The majority of the tofacitinib patients had AEs of increased creatinine levels; 18 tofacitinib patients had an AE of renal failure, acute renal failure, or acute renal insufficiency. Of these 18 patients, 16 had pre-renal etiologies such as severe dehydration, sepsis, congestive heart failure, and multi-organ failure; 1 had acute renal failure following surgery; the remaining patient had renal failure of unclear etiology that occurred after patient discontinued from study. One patient on placebo had an AE of acute renal failure.

Events occurred acutely and there was no apparent dose predilection. Resolution of renal failure occurred in a majority of patients, generally after a temporary discontinuation from study drug or permanent discontinuation from study. There was no evidence for nephrotoxicity in healthy volunteers or RA patients.

9.7.9.4. Summary of Serum Creatinine and Renal Events

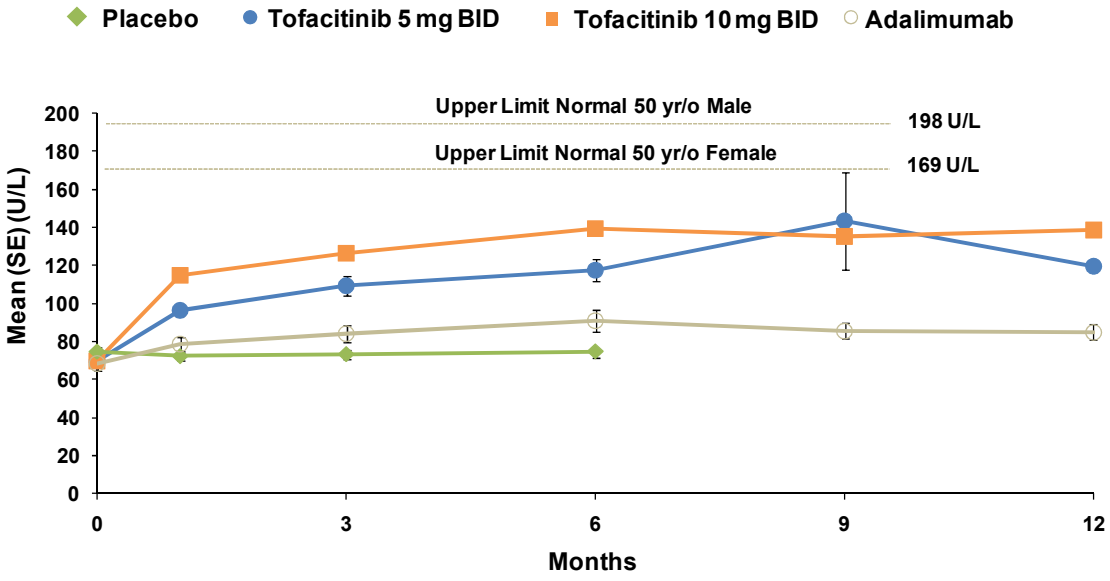
Overall, changes in creatinine associated with tofacitinib treatment are not associated with adverse effects. Adverse events of acute renal failure occurred infrequently and were generally associated with a concurrent illness. Importantly, there was no evidence of nephrotoxicity in nonclinical studies or in RA patients in the RA clinical trials.

9.7.10. Creatine Kinase and Myopathies

9.7.10.1. Creatine Kinase Levels

Dose-dependent increases in mean creatine kinase (CK) levels occurred in RA patients treated with tofacitinib during the first 6 months of therapy and plateaued thereafter (Figure 57). Mean CK levels largely remained within the normal reference range throughout the duration of treatment with tofacitinib, as illustrated by the CK upper limit of normal reference lines in Figure 57. There was no change in the mean CK levels for placebo patients over the 6 months of placebo therapy in the Phase 3 studies, whereas the adalimumab group displayed an increase in mean CK levels from baseline. In the LTE studies, there was no progressive increase in mean changes in CK levels from Phase 3 levels in the tofacitinib groups. Permanent discontinuation from study (<0.2%) and temporary discontinuation from study drug (0.2%) due to increased CK levels were infrequent in the RA program.

Figure 57. Mean Creatine Kinase Levels (IU/L) in Phase 3 Studies, by Treatment Group, (Baseline to 12 Months)



BID=twice daily; CK=creatine kinase; IU=international units; SE=standard error; U/L=units per liter; yr/o=year old

9.7.10.2. Myopathy Adverse Events

Myopathy or myositis was rarely observed in the tofacitinib RA program, and was attributable to other causes. There was no temporal association between elevated levels of CK (≥5 x ULN), as detected by routine laboratory monitoring, and reports of myopathies in the Phase 3 and LTE RA studies. Three markers of muscle catabolism (CK, LDH, and myoglobin) were measured in stored serum samples from patients enrolled in the controlled Phase 2 studies A3921025 and A3921035. No tofacitinib-associated changes in either LDH or myoglobin were found, suggesting that the changes observed in CK levels with tofacitinib treatment may not be indicative of a myopathic process.

One AE of rhabdomyolysis was reported in the tofacitinib RA Phase 3 studies in a critically ill patient with severe pulmonary hypertension, congestive heart failure, and respiratory failure. Blinded adjudication of the cause of death was performed by the external, independent CVSEAC. The cause of death was attributed to a non-cardiovascular event of infection by this committee. No AE of rhabdomyolysis was reported in the LTE studies.

9.8. Safety Summary

In the Phase 3 studies, in which tofacitinib was administered up to 12 months, safety events of interest occurred infrequently in the tofacitinib group and incidence rates for these events were similar between the 5 and 10 mg doses of tofacitinib (Table 65). Mortality rate and rate of serious adverse events were similar across the tofacitinib, adalimumab, and placebo groups.

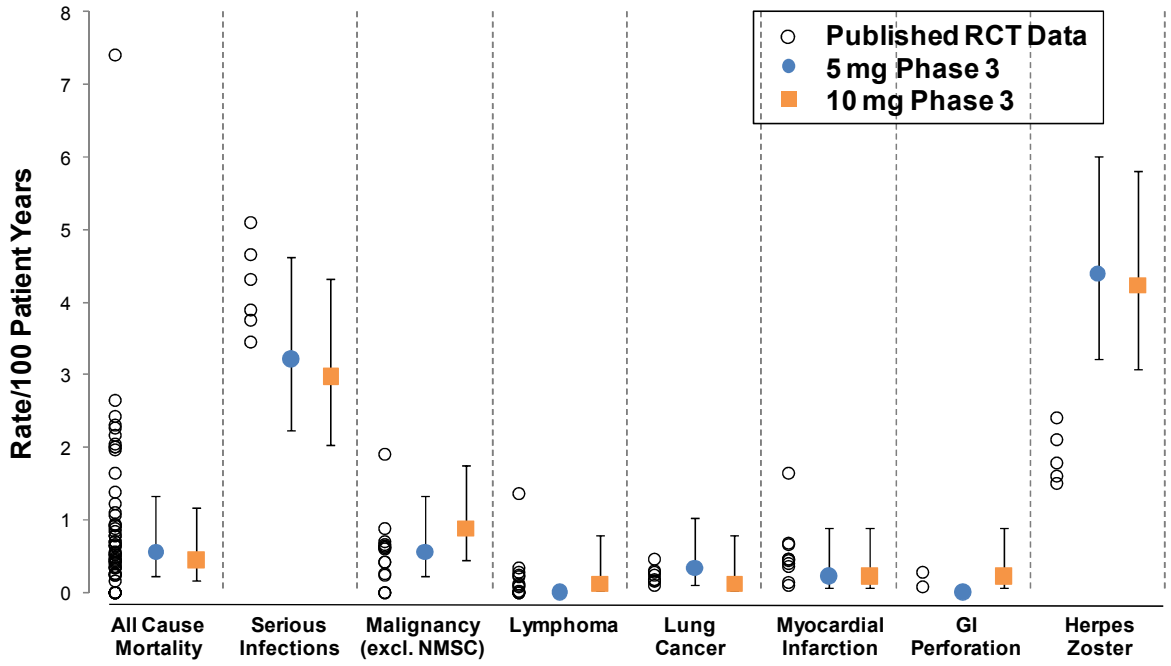
Table 65. Incidence Rates of Mortality, Serious Adverse Events, and Safety Events of Interest, Phase 3 Studies, by Treatment Group

Incidence Rates per 100 PYO (95% CI)				
Adverse Event	**Tofacitinib 5 mg** BID	**Tofacitinib 10 mg** BID	**Adalimumab** 40 mg SC q2w	**Placebo**
Mortality*	0.553 (0.230, 1.329)	0.439 (0.165, 1.171)	0.559 (0.079, 3.967)	0.494 (0.070, 3.505)
Serious Adverse Events	11.867 (9.792, 14.381)	9.758 (7.909, 12.040)	10.868 (6.932, 17.039)	15.024 (10.505, 21.488)
Serious Infection	3.217 (2.235, 4.629)	2.970 (2.037, 4.331)	1.679 (0.542, 5.206)	1.482 (0.478, 4.594)
Malignancy (excluding NMSC)	0.553 (0.230, 1.330)	0.879 (0.44, 1.757)	0.559 (0.079, 3.968)	0
Lymphoma	0	0.110 (0.015, 0.780)	0	0
Myocardial Infarction	0.221 (0.055, 0.885)	0.220 (0.055, 0.879)	1.118 (0.280, 4.469)	0
GI Perforations	0	0.220 (0.055, 0.878)	0	0
Herpes Zoster	4.391 (3.208, 6.009)	4.231 (3.079, 5.815)	2.813 (1.171, 6.759)	1.487 (0.480, 4.612)

Data as of 29 March 2011
BID=twice daily; CI=confidence interval; GI=gastrointestinal; NMSC=non-melanoma skin cancer; PYO=patient years of ovservation; q2w=every 2 weeks; SC=subcutaneously
* Mortality within 30 days of last dose of study drug

Except for herpes zoster, the incidence rates for tofacitinib treated patients for the safety events of interest in the Phase 3 studies were similar to those from clinical trial data of TNF inhibitors and other biologic DMARDs, including abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, and tocilizumab (Figure 58).

Figure 58. Safety Profile of Tofacitinib in Phase 3 Studies versus Clinical Trial Data of TNF Inhibitors and Other Biologic DMARDs



DMARDs=disease modifying anti-rheumatic drugs; GI=gastrointestinal; NMSC=non-melanoma skin cancer; RCT=randomized clinical trial

References: All Cause Mortality: Tocilizumab: U.S. FDA Drug Approval Package, Actemra, 2010; Emery, 2008; Genovese, 2008-1; Jones, 2010; Etanercept data extracted from Keystone, 2004; Weinblatt, 1999; Combe, 2006; van der Heijde, 2006; Klareskog, 2004; Bathon, 2000; Fernandez-Nebro, 2007; van Riel, 2006; Weinblatt, 2008; Emery, 2010-1;Certolizumab data extracted from Fleishmann, 2009; Smolen, 2009-2; Keystone, 2008; Adalimumab data extracted from Fernandez-Nebro, 2007; Chen, 2009; Furst, 2003; Weinblatt, 2006-1; Burmester, 2007; van de Putte, 2004; Miyasaka, 2008;Abatacept data extracted from Weinblatt, 2007; Kremer, 2006; Kremer, 2008; Schiff, 2008; Westhovens, 2009-1; Weinblatt, 2006-2; Westhovens, 2009-2; Genovese, 2008-2; Infliximab data extracted from Takeuchi, 2009; van Vollenhoven, 2009-1; St. Clair, 2004; Maini, 1999; Goekoop-Ruiterman, 2007; Fleischmann, 2005; Fernandez-Nebro, 2007; Maini, 2004; Schiff, 2008; Maini, 1998; van der Kooij, 2009; Pavelka, 2009; Abe, 2006; Rituximab data extracted from Cohen, 2006; Emery, 2006; Emery, 2010-2; Rubbert-Roth, 2010; Golimumab data extracted from U.S. FDA Drug Approval Package, Simponi, 2009; Kay, 2008; Smolen, 2009-1; Keystone, 2009; Emery, 2009; Keystone, 2010

Serious Infections: US FDA Drug Approval Package, Tocilizumab, 2010; US FDA Arthritis Advisory Committee Tocilizumab, 2001; US FDA Drug Approval Package, Adalimumab, 2008; CDER, Abatacept Medical Review and Approval Package, 2005; Gottlieb, 2011.

Malignancy (excl NMSC): TNF inhibitors data extracted from Askling, 2011; Adalimumab data extracted from Abbott Laboratories, Humira, 2011; Askling, 2011; Etancercept data extracted from Askling, 2011; Amgen Inc., 2011; Infliximab data extracted from Askling, 2011; Tocilizumab data extracted from U.S. FDA Drug Approval Package, Actemra, 2010; Abatacept data extracted from Simon, 2009; Simon, 2009; Rituximab data extracted from Askling, 2010.

Lymphoma: Abatacept=abatacept date extracted from Simon, 2009; Adalimumab data extracted from U.S. FDA Drug Briefings, Safety of TNF-Blocking Agents; Certolizumab data extracted from UCB, Inc. Cimzia Safety Information, 2011; UCB, Inc. Cimzia Safety Information, 2011; Etanercept data extracted from U.S. FDA Arthritis Advisory Committee Meeting Briefing Document, Enbrel (etanercept). Infliximab data extracted from U.S. FDA Drug Briefings, Safety of TNF-Blocking Agents; Tocilizumab data extracted from U.S. FDA Drug Approval Package, Actemra, 2010; US FDA Arthritis

Advisory Committee, Tocilizumab, 2008; Schiff, 2006.
Lung Cancer: Tocilizumab data extracted from U.S. FDA Drug Approval Package, Actemra, 2010; US FDA Arthritis Advisory Committee, Tocilizumab; Abatacept data from CDER, Abatacept Medical Review and Approval Package, 2005; Simon, 2009.
Myocardial Infarction: Tocilizumab data extracted from U.S. FDA, Drug Approval Package, Actemra, 2010; US FDA Arthritis Advisory Committee, Tocilizumab; Rituximab data extracted from U.S. FDA, Label, Rituxan; Certolizumab data extracted from Smolen, 2009-2; Adalimumab data extracted from van de Putte, 2004; Miyasaka, 2008; Abatacept data extracted from Schiff, 2008; Westhovens, 2009-1; Kremer, 2005; Infliximab data extracted from Goekoop-Ruiterman, 2007; St. Clair, 2004; Westhovens, 2006.
GI Perforation: Tocilizumab data extracted from U.S. FDA, Drug Approval Package, Actemra, 2010; US FDA Arthritis Advisory Committee, Tocilizumab; Etanercept data extracted from Combe, 2010.
Herpes Zoster: Tocilizumab data extracted from U.S. FDA, Drug Approval Package, Actemra, 2010; US FDA Arthritis Advisory Committee, Tocilizumab; Abatacept data from CDER, Abatacept Medical Review and Approval Package, 2005; Simon, 2009.

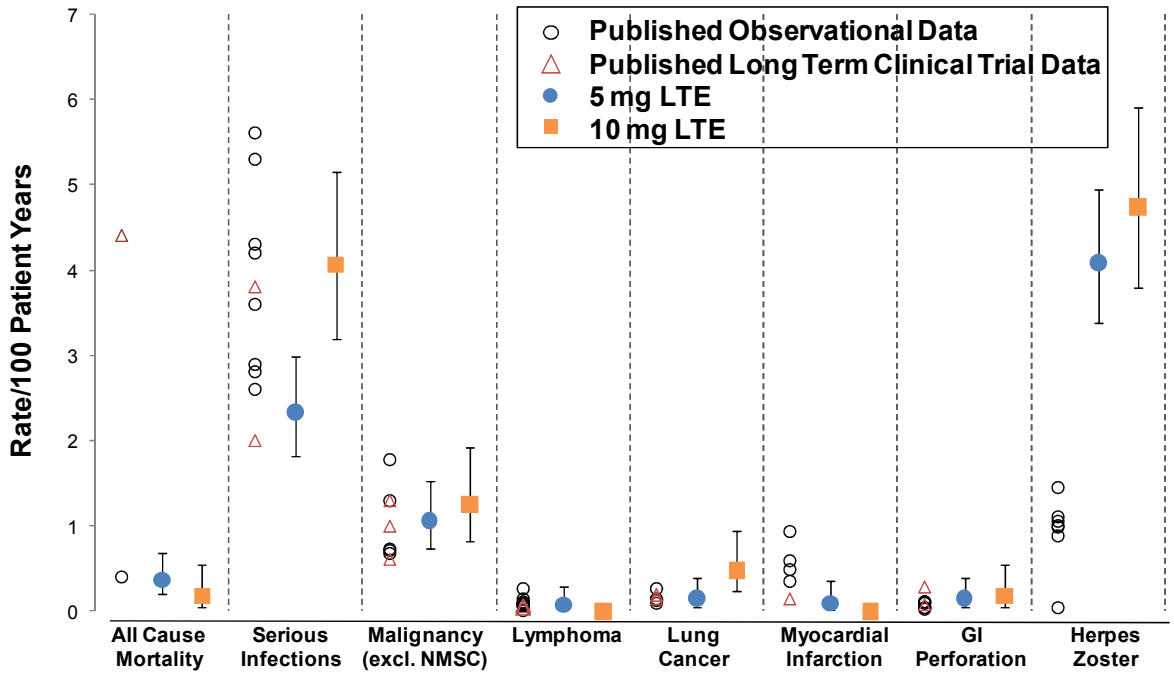
In the LTE studies, the 5 and 10 mg doses of tofacitinib differed in the incidence rates of some safety events pertaining to infection (Table 66). The rates of serious infections appeared to be increased with the 10 mg dose compared with the 5 mg dose, especially in older patients, but was consistent with published observational data for biologic DMARDs (Figure 59). Rates of herpes zoster were increased compared with published observational data for biologic DMARDs. Rates of the remaining safety events of interest were similar between the two tofacitinib doses and consistent with published registry data.

Table 66. Incidence Rates of Safety Events of Interest, Long Term Extension Studies, by Treatment Group

	Incidence Rates per 100 PYO (95% CI)		
	Tofacitinib 5 mg BID	**Tofacitinib 10 mg** BID	**All Tofacitinib**
Mortality*	0.367 (0.197, 0.682)	0.178 (0.057, 0.552)	0.295 (0.171, 0.508)
Serious Adverse Events	9.65 (8.52, 10.93)	12.32 (10.73, 14.16)	10.69 (9.74, 11.73)
Serious Infection	2.332 (1.821, 2.985)	4.058 (3.200, 5.147)	2.992 (2.521, 3.551)
Malignancy (excluding NMSC)	1.065 (0.740, 1.532)	1.248 (0.814, 1.914)	1.135 (0.860, 1.497)
Lymphoma	0.073 (0.018, 0.293)	0	0.045 (0.011, 0.181)
Lung Cancer	0.147 (0.055, 0.391)	0.475 (0.238, 0.950)	0.272 (0.155, 0.479)
Myocardial Infarction†	0.090 (0.022, 0.359)	0.000	0.051 (0.013, 0.205)
GI Perforations	0.147 (0.055, 0.391)	0.178 (0.057, 0.553)	0.159 (0.076, 0.333)
Herpes Zoster	4.089 (3.380, 4.946)	4.736 (3.794, 5.913)	4.340 (3.756, 5.015)

Data as of 29 September 2011
BID=twice daily; CI=confidence interval; GI=gastrointestinal; NMSC=non-melanoma skin cancer; PYO=patient years of ovservation; q2w=every 2 weeks; SC=subcutaneously
* Mortality within 30 days of last dose of study drug
† non-fatal myocardial infarction

Figure 59. Safety Profile of Tofacitinib 5 mg BID and 10 mg BID in the LTE Studies versus Long Term Clinical Trial and Observational Data for Biologic DMARDs



BID=twice daily; DMARDs=disease modifying anti-rheumatic drugs; GI=gastrointestinal; LTE=long term extension; NMSC=non-melanoma skin cancer
References: All Cause Mortality: Bjornadal, 2002; CDER Medical Review, Actemra
Serious Infections: Kroesen, 2003; Dixon, 2006; Carmona, 2007; BIOBADASER, ; EMECAR, ; Dixon, 2007-2; Curtis, 2007; Saillot, 2007; Favalli, 2009; Galloway, 2011; Kievit, 2011; CDER Medical Review, Actemra US FDA Drug Approval Package, Tocilizumab, 2010; Abbott Laboratories, Humira, 2011; U.S. FDA, Drug Approval Package, Adlimumab, 2008.
Malignancy: Wolfe, 2007; Simon, 2008; CDER Medical Review, Actemra; Amgen, 2011
Lymphoma: Wolfe, 2007; Wolfe, 2004; Simon, 2008; Askling, 2009; Setoguchi, 2006; CDER Medical Review, Actemra.
Lung Cancer: CDER Medical Review, Actemra; Simon, 2008.
Myocardial Infarction: CDER Medical Review, Actemra; Dixon, 2007-1
GI Perforation: Van Vollenhoven, 2009; Curtis, 2011; Combe, 2010 .
Herpes Zoster: CDER Medical Review, Actemra; Simon, 2008. Garcia-Doval, 2010.

10. RISK MANAGEMENT/PHARMACOVIGILANCE PLAN

Pfizer has developed a comprehensive risk management program, designed to facilitate timely identification and evaluation of changes in the safety profile of tofacitinib therapy, as well as risk minimization activities through labeling and communication activities. The risk management program comprises the following components:

Labeling

The proposed labeling addresses the identified and potential risks for tofacitinib, as well as special populations. It will delineate the important risks in the Warnings and Precautions and Adverse Drug Reactions sections, and provide guidance on proper patient selection and monitoring. Information on these risks is also provided in the medication guide.

- Serious Infections: the proposed labeling describes the types and incidences of serious infections reported with tofacitinib as well as biologic DMARDs. The patient counseling and patient package insert also address this potential risk. Patient selection and monitoring guidance are provided in the proposed product labeling.

- Malignancy and Lymphoproliferative Disorder: the proposed labeling describes the incidence of malignancy and lymphoproliferative disorder across the tofacitinib experience.

- Gastrointestinal Perforations: the proposed labeling describes incidence of gastrointestinal perforation events, event types and co-administered medications across the tofacitinib experience. Guidance on patient selection is provided in the proposed product labeling.

- Laboratory Parameters: the proposed labeling describes the incidence of neutropenia. Guidance for patient selection and monitoring of neutrophil counts and hemoglobin levels is provided in the proposed product labeling. Recommendations on treatment modification based on these levels are provided in the proposed labeling. The proposed labeling describes the lipid parameter elevations and provides lipid monitoring and management guidance.

- Vaccinations: the proposed labeling indicates that no data are available on the response to vaccination or on the secondary transmission of infection by live vaccines to patients receiving tofacitinib, and therefore live vaccines should not be administered to patients receiving tofacitinib.

- Hepatic Impairment: dose recommendations for tofacitinib in patients with mild or moderate hepatic impairment are provided in the proposed labeling. The proposed labeling indicates that treatment with tofacitinib is not recommended in patients with severe hepatic impairment.

- Renal Impairment: dose recommendations for tofacitinib in patients with mild or moderate renal impairment are provided in the proposed labeling. Tofacitinib dose should not exceed 5 mg BID in patients with severe renal impairment.

10.1. Pharmacovigilance Activities

- Routine pharmacovigilance and reporting:
    - The ongoing vigorous and timely collection, processing, follow-up, and analysis of individual adverse event reports, following global safety Standard Operating Procedures (SOPs). Ongoing prospective aggregate reviews, trending reviews, data mining, literature reviews are done on a regular basis as well as periodic product benefit-risk assessments and communication to regulatory agencies through Periodic Safety Update Reports and Development Safety Update Reports. These reports are comprehensive reviews of safety for the reporting period and include reviews of standard topics as well as reviews of the important identified and potential risks.

- Additional pharmacovigilance activities:
    - Ongoing and planned clinical studies:
        - Long term extension studies: will continue to assess cardiovascular safety, serious and opportunistic infections, malignancies, gastrointestinal perforations and monitor for any unidentified risks.
        - Cholesterol kinetic study: a study of the kinetics of cholesterol flux through the HDL/reverse cholesterol transport pathway in RA patients.
        - Vaccination studies: to evaluate the effect of tofacitinib on the immune response to pneumococcal and influenza vaccines as well as to further delineate the effects of tofacitinib on lymphocyte subsets. In addition there will be a substudy to prospectively collect data on herpes vaccination status in clinical and registry studies.
        - Measured renal function study: to evaluate the mechanism of serum creatinine increase in RA patients.
    - Pharmacoepidemiology studies:
        - In an effort to determine the best approach to evaluate the implications, if any, of elevated lipids seen with tofacitinib treatment in the RA program various approaches and additional study designs were assessed. In order to do this, the Sponsor considered the frequency of endpoints, feasibility of study conduct, and applicability to real-world clinical settings. Based on this evaluation, the Sponsor has determined a retrospective cohort analysis of cardiovascular events utilizing the Consortium of Rheumatology Researchers of North

America, Inc. (CORRONA) registry to be the most efficient and appropriate study design to accurately characterize risk, if any, within a reasonable timeframe.

- Objectives:
  - Engage with an RA registry to establish a cohort of patients with rheumatoid arthritis with characteristics (i.e., demographics and disease severity) similar to patients within the tofacitinib clinical trial program.
  - Estimate the rate ratio of cardiovascular events comparing tofacitinib-treated patients ("exposed") to tofacitinib non-treated patients ("unexposed" CORRONA) patients.
- Endpoints:
  - Rate ratios of cardiovascular events including: major adverse cardiovascular events, congestive heart failure, sudden death, clot-related deaths, other CV-related deaths, acute coronary syndrome, hypertension, hyperlipidemia, myocardial infarction, deep vein thrombosis, peripheral artery disease and transient ischemic attack/stroke.

- Consortium of Rheumatology Researchers of North America, Inc. (CORRONA): will be used to assess, prospectively, the rates of cardiovascular events, serious and opportunistic infections, malignancies, gastrointestinal perforations in comparison to other DMARDs among all users of tofacitinib.
- Organization of Teratology Information Specialists (OTIS): will be used to assess pregnancy outcomes.
- Three European registries are under consideration to assess, prospectively, cardiovascular safety, serious and opportunistic infections, malignancies, gastrointestinal perforations.
  - Anti-Rheumatic Therapy in Sweden Registry (ARTIS)
  - British Society for Rheumatology Biologics Register (BSRBR)
  - German Biologics Register (RABBIT)

- Risk Evaluation and Mitigation Strategy (REMS):

- Communications Plan for Healthcare Providers

  - Dear HCP Letter and communications through journals and scientific meetings, clearly outlining the important risks of tofacitinib and the importance of assessing benefit-risk for each patient both prior to initiating therapy and while continuing on therapy. The healthcare providers will include:

    - Rheumatologists and rheumatology healthcare providers.
    - Infectious disease specialists who may be consulted about serious and other important infection.
    - Gastroenterologists and hepatologists who may be consulted about gastrointestinal perforation and hepatic disease.
    - Family practitioners, general practitioners, and internal medicine specialists, and emergency medicine specialists who may treat serious infections, gastrointestinal perforations, and hepatic disease.

  - Medication Guide for Patients outlining the possible complications of tofacitinib therapy.

11. BENEFIT-RISK ASSESSMENT

Tofacitinib was studied in a comprehensive global development program covering a range of RA treatment paradigms and previous treatment experiences. The size, scope and diversity of the program has provided the data and confidence to conclude that the benefit-risk profile of tofacitinib is favorable and warrants regulatory approval for the treatment of RA.

Both tofacitinib 5 and 10 mg BID provide clinically meaningful efficacy and acceptable safety for patients with RA who are representative of the RA patient population who may be prescribed tofacitinib after approval: patients with moderately to severely active RA who had an inadequate response or intolerance to nonbiologic and/or biologic DMARDs. With its novel mechanism of action and oral route of administration, tofacitinib provides an important addition to existing treatment options. Unlike biologic DMARD therapies that are directed at extracellular targets such as individual cytokines or their receptors, tofacitinib, via JAK pathways, targets multiple cytokines that play a key role in the inflammation central to RA.

Efficacy Summary

Results from the five Phase 3 and four Phase 2 randomized, placebo controlled studies as well as data from 2 open-label LTE studies, demonstrate that tofacitinib, dosed either 5 mg or 10 mg BID, is efficacious in the treatment of adult patients with moderately to severely active RA. Significant improvement was demonstrated across multiple domains of efficacy that are clinically relevant to patients and practitioners, including signs and symptoms, inhibition of structural damage, physical function and other patient reported outcomes such as fatigue, pain, and health-related quality of life. Onset of benefit with tofacitinib use was rapid and response was durable. Improvement was demonstrated after as little as 2 weeks of treatment with tofacitinib, and sustained improvement was shown after more than 3 years of continued treatment in the LTE studies.

Consistent efficacy was demonstrated when tofacitinib was administered either as monotherapy or in combination with MTX or other nonbiologic DMARDs. Overall, consistent efficacy was demonstrated across subsets of patients evaluated according to gender, age, race, different weight or BMI groups, predefined geographical regions, baseline diseases characteristics, prior RA treatment received, and concomitant RA medications.

Safety Summary

Tofacitinib demonstrates acceptable safety in DMARD experienced patients with moderately to severely active RA, whether dosed as monotherapy or in combination with background DMARDs. Tofacitinib, like other immunomodulators used to treat RA, is associated with safety findings and potential risks. In the tofacitinib RA program this includes serious and other important infections, including tuberculosis and herpes zoster, malignancies including lymphoma, decreased neutrophil counts and neutropenia, and lipid elevations.

Tofacitinib was associated with a higher incidence of herpes zoster. The reasons for this observation are not entirely clear. The higher incidence was most notable in study participants in Asia; an association with longer duration of RA was also evident. Furthermore, continued investigation is needed to determine whether this is due solely to

drug effect or due to a combination of factors, such as apparently increased reporting rates over time of herpes zoster in both the general and RA populations.

Overall, the safety profile was similar between the 5 and 10 mg dose of tofacitinib during the Phase 3 studies. However, some adverse events, such as serious infections, appeared to be dose- and/or age-related. Dose-dependent decreases in neutrophils and changes in hemoglobin were infrequently associated with adverse events such as neutropenia or anemia. Small increases in serum creatinine and increased creatine kinase were noted; these do not appear to represent significant safety risks for tofacitinib. Increases in lipids were noted, but do not appear to increase CV risk. Cases associated with hepatic transaminase elevations were carefully evaluated; the potential for hepatic toxicity appears to be low. Laboratory changes typically normalized upon discontinuation of tofacitinib treatment.

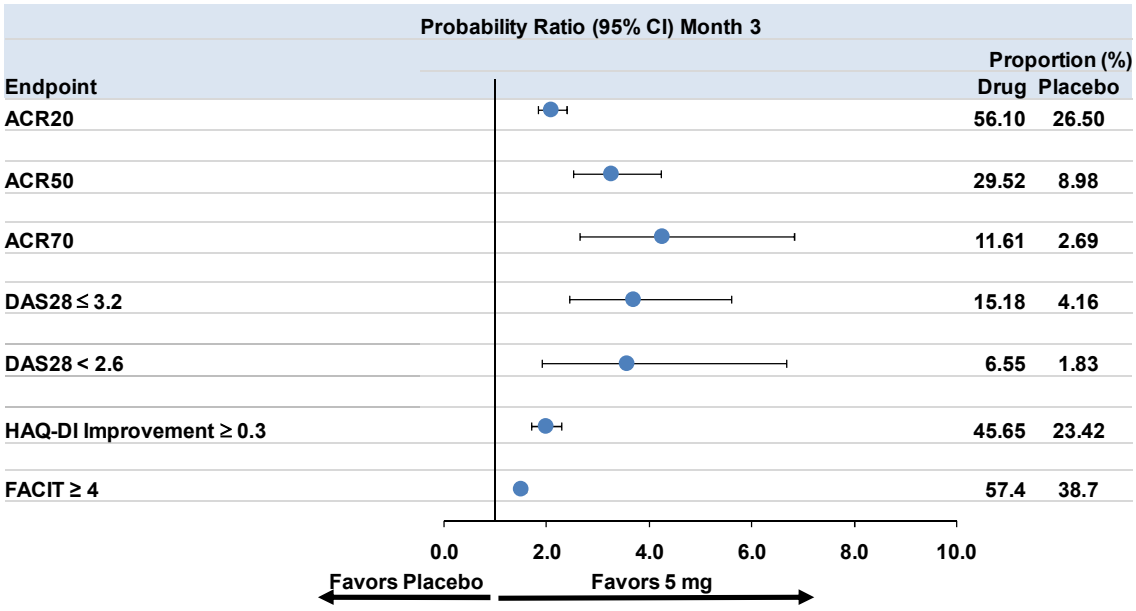
In summary, the benefit-risk profile of tofacitinib is favorable and warrants regulatory approval for the treatment of RA. Relevant efficacy and safety data are discussed below to further describe the benefit-risk profile for the 5 mg and 10 mg BID doses.

11.1. Benefit-Risk Profile of Tofacitinib 5 mg BID

Efficacy of 5 mg BID

Results from individual Phase 3 studies have demonstrated the efficacy of 5 mg BID in multiple domains that are clinically relevant to patients and practitioners. Improvements were demonstrated after as little as 2 weeks of treatment, and sustained over 3 years of continued treatment in the LTE studies. To provide an overall assessment of the magnitude of clinical efficacy, a pooled analysis of Phase 3 trials was performed for the various clinical efficacy measures after 3 months of treatment (Figure 60). Consistent with the individual study results, the proportions of responders are significantly greater for the 5 mg BID dose than for placebo across the various domains. The probability ratios (calculated as the proportion of responders to 5 mg divided by that of placebo) were higher for the more stringent measures such as ACR 50 and ACR70 and the confidence intervals excluded 1 in all cases, indicating that the 5 mg BID dose provides clinically meaningful and statistically significant benefit across all domains of clinical efficacy, relative to placebo.

Figure 60. Probability Ratios for Proportion of Patients Achieving Selected Efficacy Endpoints, Tofacitinib 5 mg BID versus Placebo (All Phase 3 Studies)



BID=twice daily; CI=confidence interval

Data from the 1044/Scan study indicates that the 5 mg BID dose inhibits the progression of structural damage (Figure 22). Although the primary endpoint, which assessed radiographic progression based on change in mean Total Sharp Score, did not show a statistically significant difference between the 5 mg dose BID and placebo, there was a 74% mean reduction in radiographic progression for the 5 mg BID dose compared to placebo. An alternative, clinically relevant and widely recognized method of assessing structural damage is the proportion of patients with no radiographic progression; this was a pre-defined secondary endpoint in the 1044/Scan study. This analysis showed that a statistically significantly higher proportion of patients achieved this goal on the 5 mg BID dose compared to placebo. In addition, a post-hoc analysis demonstrated a more pronounced treatment effect for the 5 mg BID dose relative to placebo in those patients whose prognostic factors are known to predict greater progression of joint damage. These factors include patients who were both rheumatoid factor and/or anti-cyclic citrullinated peptide (anti-CCP) positive and had a Sharp erosion score of at least 3 at baseline, and those with above the median baseline damage by Total Sharp Score. In summary, the data demonstrate that the 5 mg BID dose inhibits the progression of structural damage.

Additional perspective on the clinical benefit of the 5 mg BID dose was gained from the 1064/Standard study, in which adalimumab, administered in combination with background methotrexate, was included as an active control; this allowed estimation of the efficacy of tofacitinib relative to a widely used TNF inhibitor. The 1064/Standard study provided useful comparative data and allowed exclusion of certain differences between tofacitinib treatments and adalimumab over a range of clinical outcomes, based on 95% confidence intervals. The

efficacy of the 5 mg BID dose was similar or slightly better than that seen with adalimumab for ACR20, ACR50, and ACR70 response rates and for mean changes from baseline in disability as measured by HAQ-DI (Figure 14). This efficacy was also apparent for other efficacy endpoints, including patient-reported outcomes. The efficacy of the 5 mg BID dose is also consistent with published data from randomized clinical trials with approved biologic therapies, as described in Section 8.10.8.

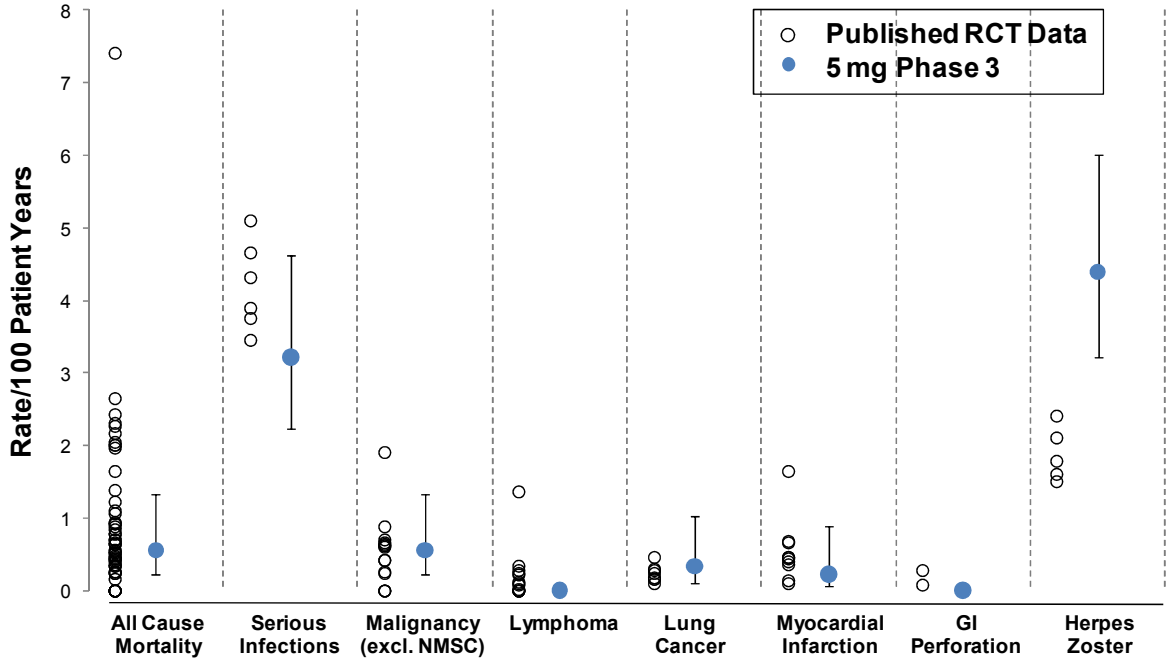
Safety of 5 mg BID

The incidence rates of important safety events with 5 mg BID tofacitinib and placebo from Phase 3 trials, as well as adalimumab from the 1064/Standard study, are shown in Table 65. Overall, these events were infrequent across all treatment arms. There were no cases of lymphoma or GI perforations in the 5 mg BID dose group in Phase 3 studies. For the remaining events, the confidence intervals for the 5 mg BID dose are contained within the relatively wide confidence intervals for the placebo and adalimumab groups.

To further contextualize the safety profile of tofacitinib, the safety data were also compared to published data for approved biologic therapies from randomized controlled trials as well as observational databases. Figure 61 shows the observed incidence rates of important safety events for the 5 mg BID dose in the Phase 3 program, overlaid against published data from RCTs of approved biologic therapies. Every effort was made to choose external comparators that were most representative and appropriate for the patient population that was studied in the clinical program. With the exception of higher rates of herpes zoster, the observed incidence rates with tofacitinib are consistent with those reported with approved biologic therapies

A similar inference can be drawn when the event rates for the 5 mg BID dose in the LTE studies are compared against those from published data from observational databases (Figure 59). The rates of key safety events for the 5 mg BID dose remain consistent with the published data, again with the exception of herpes zoster. While there are limitations associated with comparing clinical trial data to observational sources, these comparisons provide a useful way of contextualizing the safety data.

Figure 61. Safety of Tofacitinib 5 mg BID in Phase 3 Studies versus Randomized Clinical Trial Data



BID=twice daily; GI=gastrointestinal; RCT=randomized clinical trial

References: All Cause Mortality: Tocilizumab: U.S. FDA Drug Approval Package, Actemra, 2010; Emery, 2008; Genovese, 2008-1; Jones, 2010; Etanercept data extracted from Keystone, 2004; Weinblatt, 1999; Combe, 2006; van der Heijde, 2006; Klareskog, 2004; Bathon, 2000; Fernandez-Nebro, 2007; van Riel, 2006; Weinblatt, 2008; Emery, 2010-1;Certolizumab data extracted from Fleishmann, 2009; Smolen, 2009-2; Keystone, 2008; Adalimumab data extracted from Fernandez-Nebro, 2007; Chen, 2009; Furst, 2003; Weinblatt, 2006-1; Burmester, 2007; van de Putte, 2004; Miyasaka, 2008;Abatacept data extracted from Weinblatt, 2007; Kremer, 2006; Kremer, 2008; Schiff, 2008; Westhovens, 2009-1; Weinblatt, 2006-2; Westhovens, 2009-2; Genovese, 2008-2; Infliximab data extracted from Takeuchi, 2009; van Vollenhoven, 2009-1; St. Clair, 2004; Maini, 1999; Goekoop-Ruiterman, 2007; Fleischmann, 2005; Fernandez-Nebro, 2007; Maini, 2004; Schiff, 2008; Maini, 1998; van der Kooij, 2009; Pavelka, 2009; Abe, 2006; Rituximab data extracted from Cohen, 2006; Emery, 2006; Emery, 2010-2; Rubbert-Roth, 2010; Golimumab data extracted from U.S. FDA Drug Approval Package, Simponi, 2009; Kay, 2008; Smolen, 2009-1; Keystone, 2009; Emery, 2009; Keystone, 2010

Serious Infections: US FDA Drug Approval Package, Tocilizumab, 2010; US FDA Arthritis Advisory Committee Tocilizumab, 2001; US FDA Drug Approval Package, Adalimumab, 2008; CDER, Abatacept Medical Review and Approval Package, 2005; Gottlieb, 2011.

Malignancy (excl NMSC): TNF inhibitors data extracted from Askling, 2011; Adalimumab data extracted from Abbott Laboratories, Humira, 2011; Askling, 2011; Etancercept data extracted from Askling, 2011; Amgen Inc., 2011; Infliximab data extracted from Askling, 2011; Tocilizumab data extracted from U.S. FDA Drug Approval Package, Actemra, 2010; Abatacept data extracted from Simon, 2009; Simon, 2009; Rituximab data extracted from Askling, 2010.

Lymphoma: Abatacept=abatacept date extracted from Simon, 2009; Adalimumab data extracted from U.S. FDA Drug Briefings, Safety of TNF-Blocking Agents; Certolizumab data extracted from UCB, Inc. Cimzia Safety Information, 2011; UCB, Inc. Cimzia Safety Information, 2011; Etanercept data extracted from U.S. FDA Arthritis Advisory Committee Meeting Briefing Document, Enbrel (etanercept). Infliximab data extracted from U.S. FDA Drug Briefings, Safety of TNF-Blocking Agents; Tocilizumab data extracted from U.S. FDA Drug Approval Package, Actemra, 2010; US FDA Arthritis Advisory Committee, Tocilizumab, 2008; Schiff, 2006.

Lung Cancer: Tocilizumab data extracted from U.S. FDA Drug Approval Package, Actemra, 2010; US FDA Arthritis Advisory Committee, Tocilizumab; Abatacept data from CDER, Abatacept Medical Review and Approval Package, 2005; Simon, 2009.

Myocardial Infarction: Tocilizumab data extracted from U.S. FDA, Drug Approval Package, Actemra, 2010; US FDA Arthritis Advisory Committee, Tocilizumab; Rituximab data extracted from U.S. FDA, Label, Rituxan; Certolizumab data extracted from Smolen, 2009-2; Adalimumab data extracted from van de Putte, 2004; Miyasaka, 2008; Abatacept data

extracted from Schiff, 2008; Westhovens, 2009-1; Kremer, 2005; Infliximab data extracted from Goekoop-Ruiterman, 2007; St. Clair, 2004; Westhovens, 2006.
GI Perforation: Tocilizumab data extracted from U.S. FDA, Drug Approval Package, Actemra, 2010; US FDA Arthritis Advisory Committee, Tocilizumab; Etanercept data extracted from Combe, 2010.
Herpes Zoster: Tocilizumab data extracted from U.S. FDA, Drug Approval Package, Actemra, 2010; US FDA Arthritis Advisory Committee, Tocilizumab; Abatacept data from CDER, Abatacept Medical Review and Approval Package, 2005; Simon, 2009.

Summary of Benefit-Risk Profile of 5 mg BID

In summary, data collected from a robust and diverse clinical development program clearly indicate that the benefit-risk profile of the 5 mg BID dose is favorable and consistent with that of approved biologic therapies. The identified risks for tofacitinib are manageable by appropriate patient selection and screening, routine monitoring and when necessary, medical management.

11.2. Benefit-Risk Profile of Tofacitinib 10 mg BID

Efficacy of 10 mg BID

Similar to the 5 mg BID dose, Phase 3 studies have demonstrated the clinical efficacy of 10 mg BID relative to placebo in multiple domains. Since, the individual studies were not powered to formally compare 10 mg BID to 5 mg BID, Phase 3 data were pooled to improve the precision of the comparison. As shown in Figure 62 and Figure 63, the percent responders to 10 mg BID at Month 3 are greater than those of 5 mg BID across the various domains of clinical efficacy. The probability ratios indicate that 10 mg BID provides improved benefit over 5 mg BID, especially in the more stringent measures, such as ACR70 and DAS28 <2.6. For example, there is approximately a 40% greater likelihood of achieving ACR70 and DAS28 <2.6 response with the 10 mg BID dose compared with the 5 mg BID dose which is considered clinically meaningful.

Figure 62. Clinical Efficacy of Tofacitinib 5 mg BID versus Placebo and Tofacitinib 10 mg BID verus Placebo in Phase 3 Studies

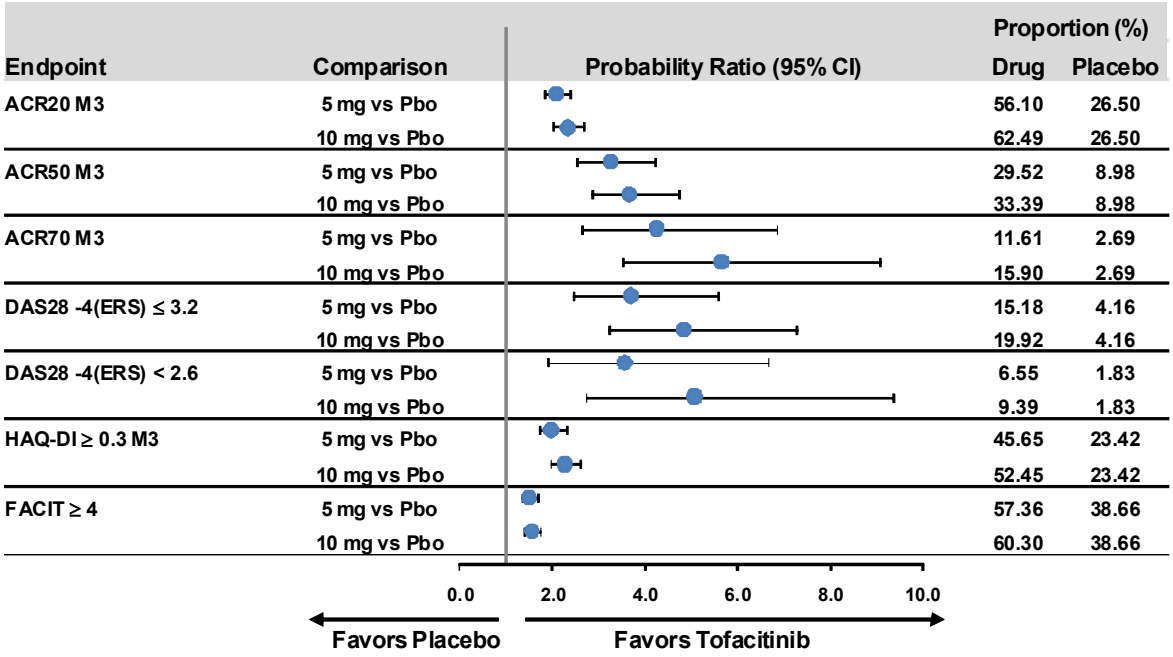
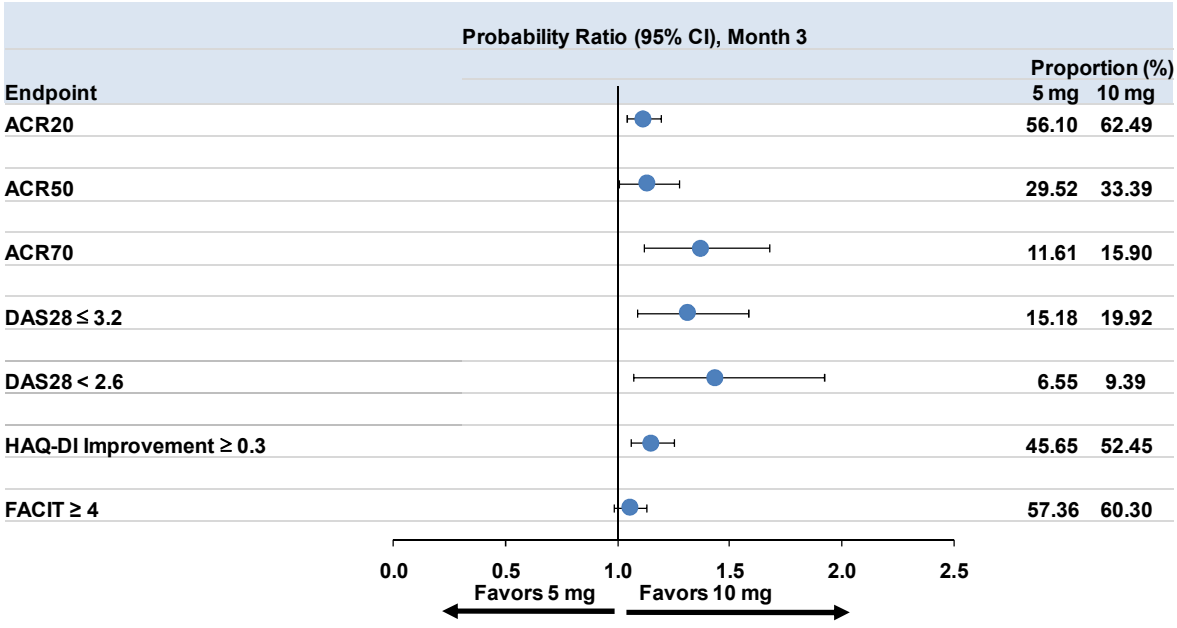


Figure 63. Clinical Efficacy of Tofacitinib 10 mg BID Compared to 5 mg BID in Phase 3 Studies



ACR=American College of Rheumatology; CI=confidence interval; DAS28=Disease activity score defined using 28 joint counts and erythrocyte sedimentation rate; FACIT= Functional Assessment of Chronic Illness Therapy – Fatigue scale; HAQ-DI= Health Assessment Questionnaire-Disability Index

Evidence for the effectiveness of the 10 mg BID dose in inhibiting the progression of structural damage was clearly demonstrated based on the primary analysis method using mean change from baseline mTSS at Month 6, and the pre-defined secondary endpoint of percentage of patients with no progression (Figure 22). Pronounced treatment effects were also observed for the 10 mg BID dose relative to placebo in those patients whose prognostic factors are known to predict greater progression of joint damage. Both tofacitinib doses demonstrated similar efficacy across the various methods of assessing radiographic progression..

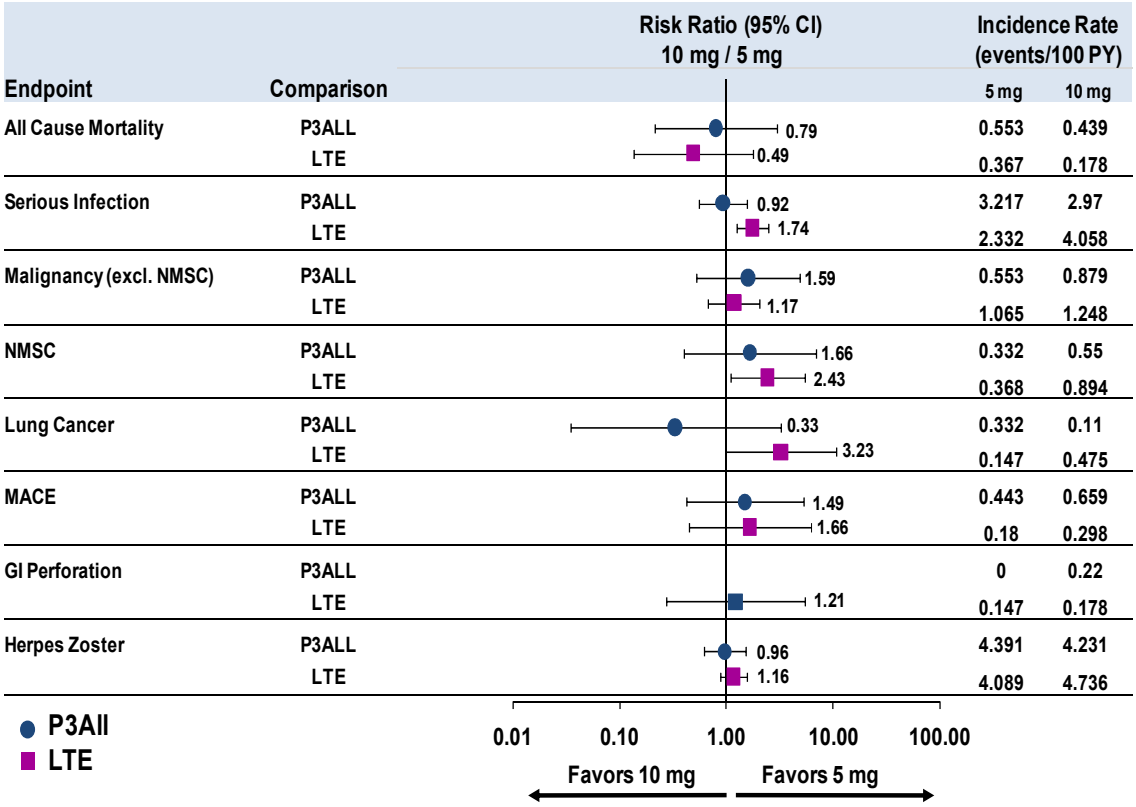
Safety of 10 mg BID

The incidence rates of important safety events with 5 and 10 mg tofacitinib, adalimumab and placebo from Phase 3 trials are shown in Table 65. Overall, the events remained infrequent across all arms, and similar between the two doses of tofacitinib, over a period of up to 12 months.

A comparison of the 5 and 10 mg tofacitinib Phase 3 data to published RCT data was previously shown in Figure 58. Additionally a comparison of the 5 and 10 mg LTE data to published observational data was shown in Figure 59. The observed incidence rates with both the 5 and 10 mg doses are consistent with those reported in RCTs and published observational data for approved biologic therapies, with the exception of increased rates of herpes zoster observed with both tofacitinib doses.

Figure 64 shows the relative risk of the 10 mg BID dose versus 5 mg BID from the Phase 3 and LTE studies. Safety and laboratory measures that show a dose dependency and thus a potential increased risk at the 10 mg BID dose include serious infections, tuberculosis, changes in hemoglobin, neutrophils and total cholesterol and LDL-c; a trend was observed towards more nonmelanoma skin cancers in patients treated with tofacitinib 10 mg BID. In the LTE studies, the incidence of lung cancer was numerically increased with the 10 mg BID dose, although the 95% CI included one. Cases of lung cancer were carefully reviewed and smoking was the only common factor (Section 9.7.2.1.2). Across the Phase 3 and LTE studies, a consistent dose effect is not observed with lung cancer. Incidence rates for the other events were similar between doses.

Figure 64. Safety of Tofacitinib 10 mg BID Compared to 5 mg BID in Phase 3 and LTE Studies



BID=twice daily; CI=confidence interval; GI=gastrointestinal; LTE=long term extension studies; MACE= major adverse cardiovascular events; NMSC=non-melanoma skin cancer; P3ALL=Phase 3 Studies; PY=patient years
Point estimates for risk ratios are shown next to the confidence intervals

Summary of Benefit-Risk Profile of 10 mg BID and Dosing Recommendation for Labeling

Data collected from this robust and diverse clinical development program indicate that the benefit-risk profile of the 10 mg BID dose is favorable and consistent with that of approved biologic therapies. Both the 5 and 10 mg BID doses demonstrated compelling efficacy, with additional benefits seen with the 10 mg BID dose, especially in the more stringent measures such as ACR70 and DAS28<2.6. As there were increased rates of some safety events in the RA program at 10 mg BID compared to 5 mg BID, the recommended dose is 5 mg BID. However, at the individual patient level, for those who do not respond adequately to the 5 mg BID tofacitinib dose, an increase to 10 mg BID may be appropriate, based on the physician's evaluation of benefit-risk in that patient. Physicians should exercise caution when considering dose escalation in elderly patients, because of the increased risk of infection in these patients, particularly at the 10 mg BID dose.

In addition, based on pharmacokinetic data, it is recommended that the dose of tofacitinib not exceed 5 mg BID in patients with severe renal or moderate hepatic impairment or in those receiving concomitant medications such as potent CYP3A4 inhibitors.

12. CONCLUSIONS

RA is a disabling, chronic and serious disease for which there is a clear medical need for additional treatment options. Tofacitinib provides an innovative oral therapeutic option and should be approved for use in patients with moderately to severely active RA who have had an inadequate response to one or more DMARDs.

- Tofacitinib is a JAK inhibitor that provides a novel mechanism for treating RA.
- It has demonstrated, through an extensive clinical program, a manageable safety profile and robust efficacy when dosed orally as 5 mg and 10 mg BID, either as monotherapy or on background DMARDs.
- The benefit-risk profile of tofacitinib is consistent with that of biologic therapies currently used in patients that have had an inadequate response to prior DMARD therapy.
- The proposed recommendations for patient management will be familiar to rheumatologists currently treating patients with existing agents for treating RA; tofacitinib should be prescribed by health care professionals with expertise in the diagnosis and use of immunomodulatory agents in RA.
- The risk management program identifies pharmacovigilance and risk management activities that will be undertaken to facilitate the safe and effective use of tofacitinib and to maintain vigilance for as of yet unidentified risks. Additionally, the risk evaluation and mitigation strategy (REMS) outlines a proposed education/communication plan for healthcare providers and patients regarding the risks associated with and the proper use of tofacitinib.

13. REFERENCES

Abasolo L, Judez E, Descalzo MA, et al. Cancer in rheumatoid arthritis: occurrence, mortality, and associated factors in a South European population. Semin Arthritis Rheum 2008; 37(6):388-97.

Abe T, Takeuchi T, Miyasaka N, et al. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. J Rheumatol 2006; 33(1):37-44.

Abbott Laboratories, ed. Humira Health Care Professionals. 2011 (copyright). Online. Abbott Laboratories.
Available:http://www.humirapro.com/Rheumatology/SafetyProfile.aspx

Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev 2005; 4(3):130-6.

Aletaha D, Smolen JS. The rheumatoid arthritis patient in the clinic: comparing more than 1300 consecutive DMARD courses. Rheumatology 2002; 41:1367-74.

Aletaha D, Neogi T, Silman AJ, et al. "2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative". Ann Rheum Dis 2010; 69 (9):1580–8.

Amgen, Inc. and Pfizer, Inc, eds. Enbrel Malignancy Rates. 2011 (copyright). Online. Amgen, Inc. and Pfizer, Inc. Available: http://www.enbrel.com/RheumPro/malignancy-rates.jspx

Antonelli, M.A., L.W. Moreland, and J.E. Brick, Herpes zoster in patients with rheumatoid arthritis treated with weekly, low-dose methotrexate. Am J Med. 1991; 90(3):295-8.

Askling J, Baecklund E, et al., Anti-tumour necrosis factor therapy in rheumatoid arthritis and risk of malignant lymphomas: relative risks and time tredns in the Swedish Biologics Register. Ann Rheum Dis 2009;68:648-653.

Askling J, Fahrbach K, Nordstrom B, et al. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiol Drug Saf 2010; 20(2):119-30.

Askling J, Fored CM, Brandt L, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis 2005; 64(10):1421-26.

Baecklund E, Askling J, Rosenquist R, et al. Rheumatoid arthritis and malignant lymphomas. Curr Opin Rheumatol 2004; 16(3):254-61.

Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its

treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum 2006; 54(3):692-701.

Baldi A, Santini M, Mellone P, et al. Mediastinal hibernoma: A case report. J Clin Pathol 2004;57(9):993-4.

Bathon JM, Fleischmann RM, van der Heijde DM, et al. Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. J Rheumatol 2006; 33(2 Feb):234-243.

Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000; 343(22):1586-93.

Bismuth J, Kofoed SC, Jensen AS, et al. Serum lipids act as inverse acute phase reactants and are falsely low in patients with critical limb ischemia. J Vasc Surg 2002; 36(5):1005-10.

Bjornadal L, Baecklund E, Yin L, et al. Decreasing mortality in patients with rheumatoid arthritis: results from a large population based cohort in Sweden, 1964-95. J Rheumatol 2002; 29(5):906-12.

Blom M, van Riel PL. Management of established rheumatoid arthritis with an emphasis on pharmacotherapy. Best Pract Res Clin Rheumatol 2007; 21(1):43-57.

Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000; 343(21):1520-8.

Bongartz T, Nannini C, Medina-Velasquez YF, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum 2010; 62(6):1583-91.

Buch MH. Sequential use of biologic therapy in rheumatoid arthritis. Curr Opin Rheumatol 2010; 22(3):321-9.

Burmester GR, Mariette X, Montecucco C, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis 2007; 66(6):732-9.

Burmester GR, Mease P, Dijkmans BAC, et al. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. Ann Rheum Dis, 2009. 68: 1863-1869.

Caillard S, Dharnidharka V, Agodoa L, et al. Posttransplant lymphoproliferative disorders after renal transplantation in the United States in era of modern immunosuppression. Transplantation 2005; 80:1233-43.

Caillard S, Lelong C, Pessioneb F, et al. Post-transplant lymphoproliferative disorders occurring after renal transplantation in adults: Report of 230 cases from the French Registry. Am J Trans 2006; 6:2735–42.

Cannon CP, Curtis SP, FitzGerald GA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet 2006; 368(9549):1771-81.

Carmona L, Abasolo L, Descalzo MA, et al. Cancer in patients with rheumatic diseases exposed to TNF antagonists. Semin Arthritis Rheum 2010;

Carmona L, Descalzo MA, Perez-Pampin E, et al. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. Ann Rheum Dis 2007; 66(7):880-5.

Carmona L, Hernandez-Garcia C, Vadillo C, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol 2003; 30(7):1436-9.

Carville A, Mansfield KG. Comparative pathobiology of macaque lymphocryptoviruses. Comp Med 2008; 58:57-67.

Centers for Disease Control, ed. Morbidity and Mortality Weekly Report. June 6, 2008; 57(05):1-30

Center for Drug Evaluation and Research. Application Number 125276, Medical Review(s). Actemra.

Center for Drug Evaluation and Research. Orencia Medical and Clinical Review and Approval Package for: Application Number BLA 125118/000 & 2005-4170S1_02_BMS-Abatacept.pptx.

Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. J Rheumatol 2005; 32(11 Nov):2130-2135.

Chen DY, Chou SJ, Hsieh TY, et al. Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. J Formos Med Assoc 2009; 108(4):310-9.

Choy E and Sattar N. Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk actions. Ann Rheum Dis 2009; 68(4):460-9.

Clegg ED, Cook JC, Chapin, RE, et al. Leydig cell hyperplasia and adenoma formation: mechanisms and relevance to humans. Reprod Toxicol 1997;11:107-21.

Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006; 54(9):2793-806.

Combe B, Codreanu C, Fiocco U, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis 2006; 65(10):1357-1362.

Combe B, Mortensen E, Baumgartner S, et al. Gastrointestinal perforations in rheumatoid arthritis subjects treated with etanercept. Ann Rheum Dis 2010; 69(3):680.

Cook JC, Foster PMD, Hardisty J, et al. Rodent Leydig cell tumorigenesis: a review of the physiology, pathology, mechanisms and relevance to humans. Crit Rev Toxicol 1999;29(2):169-261.

Curtis JR, Patkar N, Xie AY, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum 2007; 56(4):1125-33.

Curtis JR, Xie F, Chen L, et al. The incidence of gastrointestinal perforations among rheumatoid arthritis patients. Arthritis Rheum 2011; 63(2):346-51.

Cush JJ, Tugwell P, Weinblatt M, et al. US consensus guidelines for the use of cyclosporine A in rheumatoid arthritis. J Rheumatol 1999; 26(5):1176-86.

del Rincon I, Williams K, Stern MP, et al. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001; 44(12):2737-45.

Dixon, WG, Watson KD, Lunt M, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis & Rheumatism, 2006. 54(8):2368-2376.

Dixon, WG, Watson KD, Lunt M, et al. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum, 2007-1. 56(9): 2905-12.

Dixon WG, Symmons DPM, Lunt M, et al. Serious Infection Following Anti-Tumor Necrosis Factor alpha Therapy in Patients with Rheumatoid Arthritis, Lessons From Interpreting Data From Observational Studies. Arthritis & Rheumatism, 2007-2;56(9):2896-2904.

Doran MF, Pond GR, Crowson CS, et al. Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. Arthritis Rheum 2002; 46(3):625-31.

Duclos M, Gossec L, Ruyssen-Witrand A, et al. Retention rates of tumor necrosis factor blockers in daily practice in 770 rheumatic patients. J Rheumatol 2006; 33:2433-8.

Ekstrom K, Hjalgrim H, Brandt L, et al. Risk of malignant lymphomas in patients with rheumatoid arthritis and in their first-degree relatives. Arthritis Rheum 2003; 48(4):963-70.

Emery P, Breedveld F, van der Heijde D, et al. Two-Year Clinical and Radiographic Results With Combination Etanercept-Methotrexate Therapy Versus Monotherapy in Early Rheumatoid Arthritis. Arthritis Rheum 2010-1; 62(3):674-82.

Emery P, Deodhar A, Rigby WF, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis 2010-2; 69(9):1629-35.

Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: Results of a phase IIb randomized, double-blind, placebo-controlled, dose-ranging trial. Arth Rheum 2006; 54(5):1390-400.

Emery P, Fleischmann R, van der Heijde D, et al. The Effects of Golimumab on Radiographic Progression in Rheumatoid Arthritis. Results of Randomized Controlled Studies of Golimumab Before Methotrexate Therapy and Golimumab After Methotrexate Therapy. Arthritis Rheum 2011; 63(5):1200-10.

Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum 2009; 60(8):2272-83.

Evans MR, Escalante A, Battafarano DF, et al. Carotid atherosclerosis predicts incident acute coronary syndromes in rheumatoid arthritis. Arthritis Rheum 2011; 63(5):1211-20.

Favalli, EG, Desiati F, Atzeni F, et al. Serious infections during anti-TNFalpha treatment in rheumatoid arthritis patients. Autoimmun Rev, 2009. 8(3):266-73.

Fernandez-Nebro A, Irigoyen MV, Urena I, et al. Effectiveness, predictive response factors, and safety of anti-tumor necrosis factor (TNF) therapies in Anti-TNF-Naive rheumatoid arthritis. J Rheumatol 2007; 34(12):2334-2342.

Finckh A, Choi HK, Wolfe F. Progression of radiographic joint damage in different eras: trends towards milder disease in rheumatoid arthritis are attributable to improved treatment. Ann Rheum Dis 2006-1; 65(9):1192-7.

Finckh A, Liang MH, van Herckenrode CM, et al. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. Arthritis Rheum 2006-2; 55(6):864-72.

Fleischmann R, Vencovsky J, van Vollenhoven RF, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis 2009; 68(6):805-11.

Fleischmann RM, Cohen SB, Moreland LW, et al. Methotrexate dosage reduction in patients with rheumatoid arthritis beginning therapy with infliximab: the Infliximab Rheumatoid Arthritis Methotrexate Tapering (iRAMT) trial. Curr Med Res Opin 2005; 21(8):1181-90.

Franklin J, Lunt M, Bunn D, et al. Influence of inflammatory polyarthritis on cancer incidence and survival: results from a community-based prospective study. Arthritis Rheum 2007; 56(3):790-8.

Freemer MM, King TE Jr. Connective tissue disease. In: Schwarz MI, King TE Jr, editors. Interstitial Lung Disease. 4th ed. BC Decker Inc: Hamilton, ON, Canada; 2003; pp.535-98.

Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol 2003; 30(12):2563-71.

Gabriel SE, Crowson CS, Kremers HM, et al. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. Arthritis Rheum 2003; 48(1):54-8.

Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology 2011; 50(1):124-31.

García-Doval I, Pérez-Zafrilla B, Descalzo MA et al. Incidence and risk of hospitalisation due to shingles and chickenpox in patients with rheumatic diseases treated with TNF antagonists. Ann Rheum Dis 2010;69:1751-1755.

Geborek P, Bladstrom A, Turesson C, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann of Rheum Dis 2005; 64(5 May):699-703.

Genentech USA, Inc., eds. Actemra Prescribing Information. 2011 (copyright). Online. Genentech USA, Inc. Available: http://www.gene.com/gene/products/information/actemra/pdf/pi.pdf#zoom=100

Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum 2008-1; 58(10):2968-80.

Genovese MC, Schiff M, Luggen M, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis 2008-2; 67(4):547-554.

Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med 2007; 146(6):406-15.

Gonzalez A, Maradit Kremers H, Crowson CS, et al. The widening mortality gap between rheumatoid arthritis patients and the general population. Arthritis Rheum 2007; 56(11):3583-7.

Gorter SL, Bijlsma JW, Cutolo M, et al. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010; 69(6):1010-4.

Gottlieb AB, Gordon K, Giannini EH, et al. Clinical trial safety and mortality analyses in patients receiving etanercept across approved indications. J Drugs Dermatol 2011; 10(3):289-300.

Graudal N, Jürgens G. Similar effects of disease-modifying antirheumatic drugs, glucocorticoids, and biologic agents on radiographic progression in rheumatoid arthritis: meta-analysis of 70 randomized placebo-controlled or drug-controlled studies, including 112 comparisons. Arthritis Rheum 2010; 62(10):2852-63.

Greaves P. Hematopoietic and Lymphatic Systems. In: Histopathology of preclinical toxicity studies. Elsevier Press 2007.

Greenberg JD, Reed G, Kremer JM, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORONA registry. Ann Rheum Dis, 2010. 69: 380-386.

Harris ED Jr. Clinical Features of rheumatoid arthritis. In: Harris EW, Budd RC, Genovese MC, editors. Kelley's Textbook of Rheumatology. 7th ed. Vol 1. Philadelphia: Elsevier Saunders; 2005: p. 1043-78.

Hastings R, Ding TN, Butt S, et al. Neutropenia in patients receiving anti-tumor necrosis factor therapy. Arthritis Care Res 2010; 62(6):764-9.

Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum 2008; 58(1):15-25.

Hoes JN, Jacobs JW, Boers M, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 2007; 66(12):1560-7.

Jacobsson LTH, Turesson C, Gulfe A, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol 2005; 32(7):1213-1218.

Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis 2010; 69(1):88-96.

Kalksma R, Jansen TLThA, Bruyn GAW. Severe neutropenia due to naproxen therapy in rheumatoid arthritis: a case report and review of literature. Neth J Med 2002; 60(7):289-91.

Karaman MW, Herrgard S, Treiber DK, et al. A quantitative analysis of kinase inhibitor selectivity. Nat. Biotechnol. 2008;26:127-32.

Kay J, Matteson EL, Dasgupta B, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum 2008; 58(4):964-75.

Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001; 345(15):1098-104

Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis 2009; 68(6):789-96.

Keystone E, Genovese MC, Klareskog L, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Ann Rheum Dis 2010; 69(6):1129-35.

Keystone EC, Schiff MH, Kremer JM, et al. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2004; 50(2):353-63.

Keystone EC, van der Heijde D, Mason D, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum, 2008; 58(11):3319-29.

Kievit, W., et al., Long-term effectiveness and safety of TNF-blocking agents in daily clinical practice: results from the Dutch Rheumatoid Arthritis Monitoring register. Rheumatology (Oxford), 2011. 50(1):196-203.

Khurana R, Wolf R, Berney S, et al. Risk of development of lung cancer is increased in patients with rheumatoid arthritis: a large case control study in US veterans. J Rheumatol 2008; 35(9):1704-8.

Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. The Lancet, 2004. 363(9410): p. 675-681.

Kremer JM, Dougados M, Emery P, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2005; 52(8):2263-71.

Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. Ann Intern Med 2006; 144(12):865-76.

Kremer JM, Genant HK, Moreland LW, et al. Results of a two-year followup study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. Arth Rheum 2008; 58(4):953-63.

Kremers HM, Crowson CS, Therneau TM, et al. High ten-year risk of cardiovascular disease in newly diagnosed rheumatoid arthritis patients: a population-based cohort study. Arthritis Rheum 2008; 58(8):2268-74.

Kroesen, S, Widmer AF, Tryndall A, et al. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatology (Oxford), 2003. 42(5):617-21.

Kvien TK, Uhlig T, Odegard S, et al. Epidemiological aspects of rheumatoid arthritis: the gender ratio. Ann NY Acad Sci 2006; 1069:212-22.

Laas K, Roine R, Rasanen P, et al. Health-related quality of life in patients with common rheumatic diseases referred to a university clinic. Rheumatology International 2008; 29(3):267-73.

Lacaille D, Smitten A, Simon T, et al. Hospitalized infections in the abatacept rheumatoid arthritis clinical development program: an epidemiological assessment with >10,000 person-years of exposure. Journal of Rheumatology 2009; 36 (11):2568, Abstract 25.

Laine L, Connors LG, Reicin A, et al. Serious lower gastrointestinal clinical events with nonselective NSAID or coxib use. Gastroenterology 2003; 124(2):288-92.

Laine L, Curtis SP, Cryer B, et al. Assessment of upper gastrointestinal safety of etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational

Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. Lancet 2007; 369(9560):465-73.

Laine L, Curtis SP, Langman M, et al. Lower gastrointestinal events in a double-blind trial of the cyclo-oxygenase-2 selective inhibitor etoricoxib and the traditional nonsteroidal anti-inflammatory drug diclofenac. Gastroenterology 2008; 135(5):1517-25.

Linde L, Sorensen J, Ostergaard M, et al. Health-related quality of life: validity, reliability, and responsiveness of SF-36, 15D, EQ-5D [corrected], RAQoL, and HAQ in patients with rheumatoid arthritis. J Rheumatol 2008; 35(8):1528-37.

Listing J, Strangfeld A, Rau R, et al. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low-results from RABBIT, the German biologics register. Arthritis Res Ther 2006; 8(3):R66.

Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999; 354(9194):1932-9.

Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum 2004; 50(4):1051-65.

Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis & Rheumatism 1998; 41(9):1552-63.

Malysheva OA, Wahle M, Wagner U, et al. Low-dose prednisolone in rheumatoid arthritis: adverse effects of various disease modifying antirheumatic drugs. J Rheumatol 2008; 35(6):979-85.

Maradit-Kremers H, Nicola PJ, Crowson CS, et al. Patient, disease, and therapy-related factors that influence discontinuation of disease-modifying antirheumatic drugs: a population-based incidence cohort of patients with rheumatoid arthritis. J Rheumatol 2006; 33(2):248-55.

Markatseli TE, Voulgari PV, Alamanos Y, et al. Prognostic factors of radiological damage in rheumatoid arthritis: a 10-year retrospective study. J Rheumatol 2011; 38(1):44-52.

Mathers CD, Stein C, Ma Fat D, et al. Global Burden of Disease 2000: Version 2 methods and results. In: World Health Organization (WHO); Global Programme on Evidence for Health Policy Discussion Paper No. 50. Geneva, Switzerland. Oct 2002: 108 pages.

Matsumoto AK, Bathon J, Bingham CO. Rheumatoid arthritis treatment. 1998-2010 (copyright). Online. The Johns Hopkins Arthritis Center. Available: http://www.hopkins-arthritis.org/arthritis-info/rheumatoid-arthritis/rheum_treat.html

Mazzantini M, Talarico R, Doveri M, et al. Incident comorbidity among patients with rheumatoid arthritis treated or not with low-dose glucocorticoids: a retrospective study. J Rheumatol 2010; 37(11):2232-6.

McDonald, J.R., et al., Herpes zoster risk factors in a national cohort of veterans with rheumatoid arthritis. Clin Infect Dis. 2009;48(10):1364-71.

McInnes EF, Jarrett RF, Langford G, et al. Posttransplant lymphoproliferative disorder associated with primate gamma-herpesvirus in cynomolgus monkeys used in pig-to-primate renal xenotransplantation and primate renal allotransplantation. Transplantation 2002;73(1):44-52.

Mellemkjaer L, Linet MS, Gridley G, et al. Rheumatoid arthritis and cancer risk. Eur J Cancer 1996; 32A(10):1753-7.

Michaud K, Messer J, Choi HK, et al. Direct medical costs and their predictors in patients with rheumatoid arthritis. Arthritis Rheumatism 2003; 48(10):2750-62.

Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. Best Practice & Research Clinical Rheumatology, 2007. 21(5): 885-906.

Mikuls TR, Saag KG, Criswell LA, et al. Mortality risk associated with rheumatoid arthritis in a prospective cohort of older women: results from the Iowa Women's Health Study. Ann Rheum Dis 2002; 61(11):994-9.

Miyasaka N and the CHANGE Study Investigators. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Modern Rheumatology, 2008. 18(3): p. 252-262.

Moretti VM, de la Cruz M, Lackman RD. Recurrent lipoma-like hibernoma. Am J Orthop; 2010;39(6):E57-E60.

Mouterde G (Indications of glucocorticoids in early arthritis and rheumatoid arthritis: Recommendations for clinical practice based on data from the literature and expert opinion. (Mouterde G et al, J Bone Joint Spine 2010 in press).

Myasoedova E, Crowson CS, Kremers HM, et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann Rheum Dis 2011; 70(3):482-7.

Nam JL, Winthrop KL, van Vollenhoven RF, et al. Current evidence for the management of rheumatoid arthritis with biologic disease-modifying antirheumatic drugs: a systematic literature review informing EULAR recommendations for the management of RA. Ann Rheum Dis 2010;69:976-986

National Cholesterol Education Program (Expert Panel on Detection Evaluation,and Treatment of High Blood Cholesterol in Adults): Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation,

and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001;285:2486-97.

Nicola PJ, Crowson CS, Maradit-Kremers H, et al. Contribution of congestive heart failure and ischemic heart disease to excess mortality in rheumatoid arthritis. Arthritis Rheum 2006;54:60-67.

Ohashi R, Mu H, Wang X, et al. Reverse cholesterol transport and cholesterol efflux in atherosclerosis. QJM 2005;98(12):845-56.

Opar A. Kinase inhibitors attract attention as oral rheumatoid arthritis drugs. Nature Reviews Drug Discovery, 2010. 9:257-8.

Pallavicini, F.B., et al., Tumour necrosis factor antagonist therapy and cancer development: analysis of the LORHEN registry. Autoimmun Rev, 2010. 9(3): 175-80.

Pavelka K, Jarosova K, Suchy D, Senolt, et al. Increasing the infliximab dose in rheumatoid arthritis patients: a randomised, double blind study failed to confirm its efficacy. Ann Rheum Dis, 2009. 68(8): p. 1285-9.

Peltomaa, R., et al., Mortality in patients with rheumatoid arthritis treated actively from the time of diagnosis. Ann Rheum Dis, 2002. 61(10):889-94.

Prentice DE, Meikle AW. A review of drug-induced Leydig cell hyperplasia and neoplasia in the rat and some comparisons with man. Hum & Exp Toxicol 1995;14:562-72.

Prentice DE, Siegel RA, Donatsch P, et al. Mesulergine induced Leydig cell tumours, a syndrome involving the pituitary-testicular axis of the rat. Arch Toxicol Suppl 1992;15:197-204.

Radovits, BJ, Fransen J, Al Shamma S, et al. Excess mortality emerges after 10 years in an inception cohort of early rheumatoid arthritis. Arthritis Care Res (Hoboken), 2010. 62(3):362-70.

Rahman MU, Buchanan J, Doyle M, et al. Changes in patient characteristics in anti-tumor necrosis factor clinical trials for rheumatoid arthritis: results of an analysis of the literature over the past 16 years. Ann Rheum Dis 2011: doi:10.1136/ard.2010.146043

Rajakulendran, S, Gadsby K, Allen D, et al. Neutropenia while receiving anti-tumour necrosis factor treatment for rheumatoid arthritis. Ann Rheum Dis, 2006. 65(12):1678-9.

Rubbert-Roth A, Tak PP, Zerbini C, et al. Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: results of a Phase III randomized study (MIRROR). Rheumatology (Oxford), 2010. 49(9): p. 1683-93.

Salliot, C, Gossec L, Ruyssen-Witrand A, et al. Infections during tumour necrosis factor-alpha blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology (Oxford), 2007. 46(2):327-34.

Scheinfeld N. A comprehensive review and evaluation of the side effects of the tumor necrosis factor alpha blockers etanercept, infliximab and adalimumab. J Dermatolog Treat. 2004;15:280-294.

Schiff MH, Burmester GR, Kent JD, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis. 2006;65:889-94.

Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis, 2008. 67(8): 1096-1103.

Schiff M, Keiserman M, Codding C, et al. 2-year efficacy and safety in abatacept-treated patients with rheumatoid arthritis who received continuous therapy or switched from infliximab to abatacept: the ATTEST trial. Rheumatology, 2010. 49(suppl): Abstract 175.

Schmidtko J, Wang R, Wu CL, et al. Posttransplant lymphoproliferative disorder associated with Epstein-Barr-related virus in cynomolgus monkeys. Transplantation 2002;73(9):1431-9.

Schmitt C, Kuhn B, Zhang X, Kivitz AJ, Grange S. Disease-drug-drug interaction involving tocilizumab and simvastatin in patients with rheumatoid arthritis. Clin Pharmacol Ther, 2010. 89:735-740.

Setoguchi, S, Schneeweiss S, Avorn J, et al. Tumor necrosis factor-alpha antagonist use and heart failure in elderly patients with rheumatoid arthritis. Am Heart J, 2008. 156(2): 336-41.

Seong SS, Choi CB, Woo JH, et al. Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. J Rheumatol 2007; 34(4):706-11.

Shuai K, Liu B. Regulation of JAK-STAT signaling in the immune system. Nat Rev Immunol, 2003. 3(11):900-11

Silva-Lima B, Van der Laan JW. Mechanisms of nongenotoxic carcinogenesis and assessment of the human hazard. Reg Toxicol Pharmacol 2000;32:135-43.

Silverstein, FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA, 2000. 284(10):1247-55.

Simon, TA, Smitten AL, Franklin J, et al. Malignancies in the rheumatoid arthritis abatacept clinical development programme: an epidemiological assessment. Ann Rheum Dis, 2009. 68(12): 1819-26.

Singer RB. Mortality in rheumatoid arthritis patients treated with or without methotrexate. J Insur Med, 2003. 35(3-4):144-9.

Smitten AL, Simon TA, Hochberg MC, et al. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Research & Therapy 2008; 10: R45.

Smitten AL, Choi HK, Hochberg MC, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum. 2007;57(8):1431-8.

Smolen JS, Kay J, Doyle MK, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor [alpha] inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. The Lancet 2009-1; 374(9685):210-21.

Smolen JS, Landewe R, Breedveld F, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biologic disease-modifying antirheumatic drugs. Ann Rheum Dis 2010; 69:964-75.

Smolen J, Landewe RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis 2009-2; 68(6):797-804.

Sokolove J, Strand V, Greenberg JD, et al. Risk of elevated liver enzymes associated with TNF inhibitor utilization in patients with rheumatoid arthritis. Ann Rheum Dis, 2010. 69(9):1612-7.

Solomon DH, Goodson NJ, Katz JN, et al. Patterns of cardiovascular risk in rheumatoid arthritis. Ann Rheum Dis 2006; 65:1608-12.

St. Clair EW, van der Heijde MFM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: A randomized, controlled trial. Arthritis & Rheumatism 2004; 50(11):3432-43.

Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA 2009; 301(7):737-44.

Sullivan PW, Ghushchyan V, Huang XY, et al. Influence of rheumatoid arthritis on employment, function, and productivity in a nationally representative sample in the United States. J Rheumatol 2010; 37(3):544-9.

Swerdlow SH, Webber SA, Chadburn AE, et al. Post-Transplant Lymphoproliferative Disorders. In: Swedlow SH, Campo E, Harris NL, et al, editors. WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. Lyon, France: International Agency for Research on Cancer 2008: p. 343-9.

Takeuchi T, Miyasaka N, Inoue K, et al. Impact of trough serum level on radiographic and clinical response to infliximab plus methotrexate in patients with rheumatoid arthritis: results from the RISING study. Mod Rheumatol 2009; 19(5):478-87.

Tam LS, Tomlinson B, Chu TT, et al. Impact of TNF inhibition on insulin resistance and lipids levels in patients with rheumatoid arthritis. Clin Rheumatol 2007; 26(9):1495-8.

Tan H, Gruben D, French J, et al. A case study of model-based Bayesian dose response estimation. Stat Med 2011;30(21):2622-33. doi: 10.1002/sim.4276. Epub 2011 Jun 29.

UCB, Inc, eds. Cimzia Safety Information. 2011 (copyright). Online. UCB, Inc. Available: http://www.cimzia.com/rheumatoidarthritis/hcp/safety-information/malignancies.aspx

Uhlig T, Loge JH, Kristiansen S, et al. Quantification of reduced health-related quality of life in patients with rheumatoid arthritis compared to the general population. Journal of Rheumatology 2007; 34(6):1241-47.

U.S. Food and Drug Administration (FDA), Arthritis Advisory Committee (AAC). AAC meeting to discuss BLA 125276 for tocilizumab for the treatment of moderately to severely active rheumatoid arthritis (RA) Available: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4371b1-01-FDA.pdf 26 Jun 2008.

U.S. Food and Drug Administration, ed. Drug Approval Package, Simponi (golulimumab) injection. Medical Review, Table 7.3.1. 5 June 2009 (date created). Online. U.S. Food and Drug Administration. Available: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/125289s0000TOC.cfm

U.S. Food and Drug Administration, ed. Drug Approval Package, Actemra (tocilizumab) injection. Medical Review, Table 4 and Table 6. 9 March 2010 (date created). Online. U.S. Food and Drug Administration. Available: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125276s000MedR.pdf

U.S. Food and Drug Administration, ed. Drug Approval Package, Humira (adalimumab) injection. Medical Review, Table 74. 18 January 2008 (date created). Online. U.S. Food and Drug Administration. Available: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/125057s110TOC.cfm

U.S. Food and Drug Administration, ed. Drug Label, Rituxan (rituximab) injection. 2011 (date revised). Online. Biogen Idec Inc. and Genentech, Inc. Available: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103705s5311lbl.pdf

U.S. Food and Drug Administration, ed. Drug Label, Remicade (infliximab) injection. February 2010 (date revised). Online. Centocor Ortho Biotech, Inc. Available: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103772s5281lbl.pdf

U.S. Food and Drug Administration, ed. Drug Briefings, Safety of TNF-Blocking Agents. Online. U.S. Food and Drug Administration. Available: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3930B1_01_B-TNF.Briefing.htm

U.S. Food and Drug Administration, ed. Arthritis Advisory Committee Meeting Briefing Document, Enbrel (etanercept). Online. U.S. Food and Drug Administration. Available: http://www.fda.gov/ohrms/dockets/ac/03/briefing/3930B1_03_B-Amgen-Enbrel-Errata.pdf

van de Putte LBA, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Annals of the Rheumatic Diseases 2004; 63(5):508-16.

van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis & Rheumatism 2006; 54(4):1063-74.

van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis 2009; 68(6):914-21.

Van Doornum S, McColl G and Wicks IP. Accelerated atheroscelrosis. An extraarticular feature of rheumatoid arthritis? Arthritis Rheum 2002; 46(4):862-73.

van Riel PLCM, Taggart AJ, Sany J, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Annals of the Rheumatic Diseases, 2006. 65(11): p. 1478-1483.

van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet, 2009-1. 374(9688): p. 459-66.

van Vollenhoven RF, Keystone EC, Furie R, et al. Gastrointestinal safety in patients with rheumatoid arthritis treated with tocilizumab: data from Roche clinical trials [abstract]. Arthritis Rheum 2009-2; 60 Suppl:10:1613 DOI: 10.1002/art.226687.

Veetil BMA, Matteson EL, Gabriel SE, et al. Incidence and time trends of herpes zoster in rheumatoid arthritis: a population based cohort study: data from Mayo Clinic [scientific poster]. Mayo Foundation for Medical Education and Research, 2011.

Ware JE, Jr., Snow KK, Kosinski M, et al. SF-36 Health Survey Manual and Interpretation Guide. Boston, MA: The Health Institute, New England Medical Center, 1993.

Watson DJ, Rhodes T and Guess HA. All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis in the UK General Practice Research Database. J Rheumatol 2003; 30(6):1196-1202.

Weinblatt ME, Keystone EC, Furst DE, et al. Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. Ann Rheum Dis 2006-1: 65(6):753-9.

Weinblatt ME, Kremer JM, Bankhurst AD, et al. A Trial of Etanercept, a Recombinant Tumor Necrosis Factor Receptor:Fc Fusion Protein, in Patients with Rheumatoid Arthritis Receiving Methotrexate. N Engl J Med 1999; 340(4):253-9.

Weinblatt M, Combe B, Covucci A, et al. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. Arthritis Rheum 2006-2; 54(9):2807-16.

Weinblatt M, Schiff M, Goldman A, et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. Annals of the Rheumatic Diseases 2007; 66(2):228-34.

Weinblatt ME, Schiff MH, Ruderman EM, et al. Efficacy and safety of etanercept 50 mg twice a week in patients with rheumatoid arthritis who had a suboptimal response to etanercept 50 mg once a week: results of a multicenter, randomized, double-blind, active drug-controlled study. Arthritis Rheum 2008: 58(7):1921-30.

Westhovens R, Kremer JM, Moreleand LW, et al. Safety and efficacy of the selective costimulation modulator abatacept in patients with rheumatoid arthritis receiving background methotrexate: a 5-year extended phase IIB study. J Rheumatol, 2009-1; 36(4):736-42.

Westhovens R, Robles M, Ximenes AC, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis 2009-2; 68(12):1870-77.

Westhovens R, Yocum D, Han J, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum 2006; 54(4):1075-86.

Wolfe F, Freundlich B, and Straus WL. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. J Rheumatol 2003; 30(1):36-40.

Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. J Rheumatol 1996; 23(8):1407-1417.

Wolfe F, and Hawley DJ. The comparative risk and predictors of adverse gastrointestinal events in rheumatoid arthritis and osteoarthritis: a prospective 13 year study of 2131 patients. J Rheumatol 2000; 27(7):1668-73.

Wolfe F, and Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum 2004; 50(6):1740-51.

Wolfe F, and Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. Arthritis Rheum 2007; 56(9): 2886-95.

Wolfe F, Michaud K, and Chakravarty EF. Rates and predictors of herpes zoster in patients with rheumatoid arthritis and non-inflammatory musculoskeletal disorders. Rheumatology 2006; 45(11):1370-5.

Wolfe F, Mitchell DM, Sibley JT, et al. The mortality of rheumatoid arthritis. Arthritis Rheum 1994; 37(4):481-94.

World Health Organization, ed. The Global Burden of Disease 2004 Update. Online. World Health Report 2004. Available: http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf

Yamada T, Nakajima A, Inoue E, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis in Japan. Ann Rheum Dis 2006; 65(12):1661-3.

Yelin E, and Wanke LA. An assessment of the annual and long-term direct costs of rheumatoid arthritis: the impact of poor function and functional decline. Arthritis Rheum 1999; 42(6):1209-18.

Young, A, Koduri G, Batley M, et al. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology 2007; 46(2):350-7.

14. APPENDICES

14.1. Appendix I: Adverse Event Tables

Table 67. Treatment-Emergent Adverse Events by Decreasing Frequency* (All Causality, ≥2% in Any Treatment Group) in Phase 3 Studies (3 to 6 Months): Number (%) of Patients

	Tofacitinib				
Preferred Term	**5 mg BID n=1451**	**10 mg BID n=1439**	**All Doses n=2890**	**Placebo n=221**	**ADA n=204**
Total patients with adverse events	***579 (39.9)***	***556 (38.6)***	***1135 (39.3)***	***58 (26.2)***	***68 (33.3)***
Upper respiratory tract infection	54 (3.7)	41 (2.8)	95 (3.3)	0	2 (1.0)
Nasopharyngitis	32 (2.2)	30 (2.1)	62 (2.1)	5 (2.3)	3 (1.5)
Urinary tract infection	25 (1.7)	24 (1.7)	49 (1.7)	2 (0.9)	6 (2.9)
Back pain	13 (0.9)	22 (1.5)	35 (1.2)	3 (1.4)	5 (2.5)
Pharyngitis	4 (0.3)	6 (0.4)	10 (0.3)	0	4 (2.0)

ADA=adalimumab; BID=twice daily.
*decreasing frequency to tofacitinib all doses group.
Except for the total number of adverse events, patients are counted only once per treatment in each row.

Table 68. Treatment-Emergent Adverse Events by Decreasing Frequency* (All Causality, ≥2% in Any Treatment Group) in Phase 3 (>6 Months): Number (%) of Patients

	Tofacitinib			
Preferred Term	**5 mg BID n=1056**	**10 mg BID n=1046**	**All Doses n=2102**	**ADA n=204**
Total patients with adverse events	***445 (42.1)***	***478 (45.7)***	***923 (43.9)***	***83 (40.7)***
Upper respiratory tract infection	36 (3.4)	42 (4.0)	78 (3.7)	4 (2.0)
Nasopharyngitis	33 (3.1)	30 (2.9)	63 (3.0)	5 (2.5)
Bronchitis	21 (2.0)	28 (2.7)	49 (2.3)	4 (2.0)
Urinary tract infection	15 (1.4)	31 (3.0)	46 (2.2)	5 (2.5)
Herpes zoster	20 (1.9)	22 (2.1)	42 (2.0)	4 (2.0)

ADA=adalimumab, BID=twice daily.
*decreasing frequency by tofacitinib all doses group.
Except for the total number of adverse events, patients are counted only once per treatment in each row.

14.2. Appendix II: Deaths

Table 69. All Deaths in RA Phase 3 Studies

Treatment Group	Gender/ Age (yr)[a]	Day of Death[b]	Total Exposure to Study Drug (days)[c]	Cause of Death or Fatal Event (Preferred Term)/ Adjudication by CV SEAC
Tofacitinib 5 mg BID				
	M/73	216 (13 days poststudy)	203	Pneumonia / Non-cardiovascular: Infection
	M/74	50 (8 days poststudy)	42	Acute respiratory distress syndrome Pneumonia viral Respiratory failure / Non-cardiovascular: Infection
	F/69	332 (25 days poststudy)	307	Lung cancer metastatic Hepatic failure Renal failure/ N/A
	F/75	72 (31 days poststudy)	41	Multi-organ failure / Non-cardiovascular: Infection
	M/81	192 (22 days poststudy)	170	Haemorrhage intracranial Traumatic brain injury / Non-cardiovascular: Trauma
	M/49	345 (54 days poststudy)	298	Rheumatoid arthritis Interstitial lung disease/ Non-cardiovascular: Infection
	F/54	401 (35 days poststudy)	366	Pneumonia Sepsis syndrome / N/A
Tofacitinib 10 mg BID				
	M/74	165 (8 days poststudy)	157	Aspiration (verbatim: aspirated the glycerin stick)/ Non-cardiovascular: Other

Table 69. All Deaths in RA Phase 3 Studies

Treatment Group	Gender/ Age (yr)[a]	Day of Death[b]	Total Exposure to Study Drug (days)[c]	Cause of Death or Fatal Event (Preferred Term)/ Adjudication by CV SEAC
	F/78	107 (5 days poststudy)	102	Cardiac arrest Hyperkalaemia / Cardiac death: Coronary heart disease
	M/58	374 (17 days poststudy)	357	Respiratory failure / Non-cardiovascular: Infection
	M/37	174 (therapy stop date unknown)	N/A	Cardiac failure acute / Non-cardiovascular: Other, noncardiac vascular death
Placebo to Tofacitinib 10 mg BID				
	F/51	132 (1 day post tofacitinib, 48 days post placebo)	47 (to tofacitinib)	Pulmonary embolism / Unknown reason
Placebo				
	F/51	204 (therapy stop date unknown)	N/A	Bacterial sepsis Cardiac arrest Diabetic nephropathy Hydronephrosis Renal failure acute Pyelonephritis Uraemic encephalopathy/ Non-cardiovascular: Other
Adalimumab				
	M/68	72 (1 day poststudy)	71	Cardiac arrest/ Cardiac death: Sudden cardiac death
	M/62	480 (227 days post adalimumab)	253	Non-small cell lung cancer
	F/64	459 (276 days post adalimumab)	183	Hypoplastic marrow

Table 69. All Deaths in RA Phase 3 Studies

Treatment Group	Gender/ Age (yr)[a]	Day of Death[b]	Total Exposure to Study Drug (days)[c]	Cause of Death or Fatal Event (Preferred Term)/ Adjudication by CV SEAC

Data as of 29 September 2011
BID=twice daily, CV SEAC=Cardiovascular Safety Endpoint Adjudication Committee, N/A=not available, poststudy=after discontinuation of study treatment (therapy stop date), SAE=serious adverse event.
a. Age at date of SAE onset.
b. Day of death is calculated as date of death minus date of first active therapy minus one.
c. Total exposure calculated as day of death minus (date of death minus therapy stop date).

Table 70. All Deaths in Long-Term Extension Studies

Treatment Group	Gender/ Age (yr)[a]	Day of Death[b]	Total Exposure to Tofacitinib (days)[c]	Cause of Death or Fatal Event (Preferred Term)/ Adjudication by CV SEAC
Tofacitinib 5 mg BID				
	M/49	1188 (1 day poststudy)	1187	Arrhythmia Coronary artery disease/ N/A
	F/69	525 (113 days poststudy)	412	Lung neoplasm malignant/ N/A
	F/60	638 (33 days poststudy)	605	Brain injury/ Non-cardiovascular: Other
	M/57	247	247	Arrhythmia Hypertension Arteriosclerosis/ N/A
	M/46	683 (19 days poststudy)	664	Appendicitis Cardiac arrest Respiratory arrest Sepsis/ Noncardiovascular : Infection
	F/70	182 (92 days poststudy)	90	Multi-organ failure/ N/A

Table 70. All Deaths in Long-Term Extension Studies

Treatment Group	Gender/ Age (yr)[a]	Day of Death[b]	Total Exposure to Tofacitinib (days)[c]	Cause of Death or Fatal Event (Preferred Term)/ Adjudication by CV SEAC
	F/72	772 (2 days poststudy)	770	Chronic obstructive pulmonary disease Respiratory failure/ Noncardiovascular: Other
	M/62	516 (34 days poststudy)	482	Lung neoplasm malignant Metastases to liver/ Noncardiovascular: Cancer
	F/61	835 (771 days poststudy)	64	Breast cancer metastatic Neoplasm malignant/ N/A
	F/62	501 (therapy stop date unknown)	N/A	Cardio-respiratory arrest/ Cardiac: Sudden cardiac death
	F/70	31 (therapy stop date unknown)	N/A	N/A/ N/A
	F/74	722 (14 days poststudy)	708	Cerebrovascular accident/ Unknown reason
	M/78	141 (therapy stop date unknown)	N/A	Colon cancer/ N/A
	M/71	836 (therapy stop date unknown)	N/A	Completed suicide Gunshot wound Brain contusion/ N/A
	F/64	229 (37 days poststudy)	192	Pneumonia Renal failure acute/ Noncardiovascular : Infection

Table 70. All Deaths in Long-Term Extension Studies

Treatment Group	Gender/ Age (yr)[a]	Day of Death[b]	Total Exposure to Tofacitinib (days)[c]	Cause of Death or Fatal Event (Preferred Term)/ Adjudication by CV SEAC
	F/58	913 (327 days poststudy)	586	Malignant ascites Ovarian cancer Metastases to lymph nodes Omentum neoplasm Cachexia Ovarian cancer recurrent Sepsis Pneumonia Malignant pleural effusion/ N/A
	F/59	230 (69 days poststudy)	161	Thrombotic thrombocytopenia purpura Multi-organ failure/ N/A
	F/66	1142	1142	Sepsis Pneumonia N/A
	F/73	821 (10 days post study)	811	Gallbladder cancer / N/A
	F/68	220 (38 days post study)	182	Synovial sarcoma/ NR
Tofacitinib 10 mg BID				
	M/35	1	1	Completed suicide/ N/A
	M/67	15 (4 days poststudy)	11	Acute respiratory distress syndrome Arteriosclerosis Bronchopneumonia Cardiac failure Cardiopulmonary failure Circulatory collapse Pleurisy Renal failure Septic shock/ Noncardiovascular : Infection

Table 70. All Deaths in Long-Term Extension Studies

Treatment Group	Gender/ Age (yr)[a]	Day of Death[b]	Total Exposure to Tofacitinib (days)[c]	Cause of Death or Fatal Event (Preferred Term)/ Adjudication by CV SEAC
	F/64	107 (39 days poststudy)	68	Hepatic neoplasm malignant Lung neoplasm malignant/ N/A
	F/58	386 (5 days post study)	381	Cardio-respiratory arrest/ N/A
	M/64	148 (37 days post study)	111	Lung neoplasm malignant/ NR
	F/80	448 (100 days post study)	348	Lung adenocarcinoma/ Noncardiovascular death: cancer
	M/64	281 (87 days post study)	194	Small cell lung cancer metastatic/ N/A
	M/71	188 (84 days post study)	104	Pneumonia/ NR

Data as of 29 September 2011
BID=twice daily; CV SEAC=Cardiovascular Safety Endpoint Adjudication Committee; N/A=not available; poststudy=after discontinuation of study treatment (therapy stop date); SAE=serious adverse event.
a. Age at date of death.
b. Day of death is calculated as date of death minus date of first active therapy minus one.
c. Total exposure calculated as day of death minus (date of death minus therapy stop date).

14.3. Appendix III: Serious Adverse Event Tables

Table 71. Serious Adverse Events (All Causality) in Phase 3 Studies, 0-3 Months

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Placebo	Adalimumab
Total preferred term events	*48*	*46*	*94*	*32*	*6*
Total number of cases	*38*	*35*	*73*	*24*	*6*
Total number of patients with serious adverse events	*38*	*33*	*71*	*24*	*5*
Blood and lymphatic system disorders					
Disseminated intravascular coagulation	1	0	1	0	0
Cardiac disorders					
Acute myocardial infarction	0	0	0	0	1
Angina pectoris	2	0	2	0	0
Atrioventricular block complete	0	0	0	1	0
Bradycardia	1	0	1	0	0
Cardiac arrest	0	0	0	0	1
Myocardial infarction	0	1	1	0	0
Ear and labyrinth disorders					
Vertigo	0	2	2	0	0
Eye disorders					
Ulcerative keratitis	0	1	1	0	0
Gastrointestinal disorders					
Anal polyp	0	1	1	0	0
Constipation	0	1	1	0	0
Diverticular perforation	0	1	1	0	0
Pancreatitis	1	0	1	0	0
Salivary gland calculus	0	0	0	1	0
Vomiting	0	1	1	0	0
General disorders and administration site conditions					
Chest pain	1	0	1	0	0
Device breakage	0	1	1	0	0
Drug ineffective [a]	0	0	0	1	0
Impaired healing	1	0	1	0	0

Table 71. Serious Adverse Events (All Causality) in Phase 3 Studies, 0-3 Months

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Placebo	Adalimumab
Multi-organ failure	1	0	1	0	0
Non-cardiac chest pain	0	1	1	0	0
Pyrexia	1	0	1	0	0
Hepatobiliary disorders					
Biliary dyskinesia	0	0	0	1	0
Cholecystitis acute	1	1	2	0	1
Cholelithiasis	2	0	2	0	0
Liver disorder	0	0	0	1	0
Infections and infestations					
Abscess jaw	1	0	1	0	0
Arthritis bacterial	0	1	1	0	0
Bronchitis	1	0	1	0	0
Cellulitis	2	1	3	0	0
Cholecystitis infective	1	0	1	0	0
Cytomegalovirus viraemia	0	1	1	0	0
Dengue fever	1	0	1	0	0
Diabetic foot infection	0	1	1	0	0
Gastroenteritis	0	0	0	1	0
Herpes zoster	0	1	1	0	0
Herpes zoster disseminated	1	0	1	0	0
Influenza	0	1	1	0	0
Labyrinthitis	0	1	1	0	0
Liver abscess	0	1	1	0	0
Osteomyelitis	1	0	1	0	0
Pneumocystis jiroveci pneumonia	1	0	1	0	0
Pneumonia	1	2	3	0	0
Pneumonia viral	1	0	1	0	0
Sialoadenitis	0	1	1	1	0
Urinary tract infection	0	1	1	0	0
Injury, poisoning and procedural complications					
Ankle fracture	1	0	1	0	0
Concussion	0	1	1	0	0
Contusion	0	0	0	2	0
Femur fracture	1	1	2	0	1
Foot fracture	0	0	0	1	0

Table 71. Serious Adverse Events (All Causality) in Phase 3 Studies, 0-3 Months

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Placebo	Adalimumab
Humerus fracture	1	0	1	0	0
Joint sprain	0	1	1	1	0
Ligament sprain	0	1	1	0	0
Muscle rupture	0	1	1	0	0
Road traffic accident	0	1	1	1	0
Tendon rupture	0	1	1	0	0
Thoracic vertebral fracture	1	0	1	0	0
Tibia fracture	0	0	0	1	0
Metabolism and nutrition disorders					
Dehydration	0	0	0	1	0
Diabetes mellitus	1	0	1	0	0
Hypoglycaemia	1	1	2	0	0
Hyponatraemia	0	0	0	1	0
Musculoskeletal and connective tissue disorders					
Arthralgia	1	0	1	0	0
Arthropathy	1	0	1	0	0
Back pain	1	0	1	0	0
Fracture nonunion	0	1	1	0	0
Inguinal mass	0	0	0	1	0
Rheumatoid arthritis	0	0	0	4	0
Spinal column stenosis	0	1	1	0	0
Tendon disorder	1	0	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Basal cell carcinoma	1	0	1	0	0
Breast cancer	0	1	1	0	0
Gastric cancer	1	0	1	0	0
Hair follicle tumour benign	1	0	1	0	0
Metastases to lymph nodes	1	0	1	0	0
Metastatic neoplasm	0	1	1	0	0
Metastatic renal cell carcinoma	1	0	1	0	0
Ovarian germ cell teratoma benign	0	1	1	0	0

Table 71. Serious Adverse Events (All Causality) in Phase 3 Studies, 0-3 Months

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Placebo	Adalimumab
Squamous cell carcinoma of the cervix	0	1	1	0	0
Thyroid adenoma	0	1	1	0	0
Nervous system disorders					
Carotid artery disease	0	1	1	0	0
Carotid artery stenosis	0	1	1	0	0
Cerebrovascular accident	2	0	2	0	0
Dysarthria	0	0	0	1	0
Epilepsy	0	0	0	1	0
Grand mal convulsion	0	0	0	1	0
Polyneuropathy	0	0	0	1	0
Transient ischaemic attack	0	0	0	1	0
Pregnancy, puerperium and perinatal conditions					
Abortion spontaneous	0	0	0	1	0
Unintended pregnancy	0	0	0	1	0
Renal and urinary disorders					
Glomerular vascular disorder	0	0	0	1	0
IgA nephropathy	0	0	0	0	1
Reproductive system and breast disorders					
Endometriosis	1	0	1	0	0
Menorrhagia	0	0	0	1	0
Respiratory, thoracic and mediastinal disorders					
Acute respiratory distress syndrome	1	0	1	0	0
Chronic obstructive pulmonary disease	1	1	2	0	0
Hydrothorax	0	0	0	0	1
Pleuritic pain	1	0	1	0	0
Pulmonary embolism	0	0	0	1	0
Sleep apnoea syndrome	0	0	0	1	0

Table 71. Serious Adverse Events (All Causality) in Phase 3 Studies, 0-3 Months

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Placebo	Adalimumab
Skin and subcutaneous tissue disorders					
Angioedema	1	0	1	0	0
Prurigo	1	0	1	0	0
Skin ulcer	1	0	1	0	0
Social circumstances					
Breast prosthesis user	0	1	1	0	0
Surgical and medical procedures					
Abdominoplasty	0	1	1	0	0
Vascular disorders					
Aortic aneurysm	0	1	1	0	0
Deep vein thrombosis	0	0	0	1	0
Hypotension	1	0	1	0	0
Peripheral vascular disorder	0	1	1	0	0
Venous thrombosis	0	1	1	0	0

Data as of 29 March 2011
Total number of patients with serious adverse events: 100.
A case is a single event or a series of related events not separated in time occurring in a single patient.
A case coded to several body systems may be counted as separate events and may include both serious and nonserious events.

Table 72. Serious Adverse Events (All Causality) in Phase 3 Studies, 3 - 6 months

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Placebo	Adalimumab
Total preferred term events	*47*	*52*	***99***	***15***	*3*
Total number of cases	*40*	*35*	***75***	*7*	*2*
Total number of patients with serious adverse events	*40*	*33*	***73***	*7*	*2*
Blood and lymphatic system disorders					
Anaemia	0	2	2	0	0
Leukocytosis	1	0	1	0	0
Thrombocytopenia	2	0	2	0	0
Cardiac disorders					

Table 72. Serious Adverse Events (All Causality) in Phase 3 Studies, 3 - 6 months

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Placebo	Adalimumab
Acute myocardial infarction	1	0	1	0	0
Atrial fibrillation	0	1	1	0	0
Cardiac arrest	0	1	1	1	0
Cardiac failure acute	0	1	1	0	0
Cardiac failure congestive	0	3	3	0	0
Coronary artery disease	1	0	1	0	0
Myocardial infarction	0	1	1	0	0
Myocardial ischemia	0	0	0	0	1
Pericarditis	0	1	1	0	0
Eye disorders					
Retinal detachment	0	1	1	0	0
Gastrointestinal disorders					
Colitis	1	0	1	0	0
Nausea	0	1	1	0	0
Pancreatitis	1	0	1	0	0
Peptic ulcer haemorrhage	0	1	1	0	0
Vomiting	0	1	1	0	0
General disorders and administration site conditions					
Asthenia	0	1	1	0	0
Multi-organ failure	0	1	1	0	0
Pyrexia	0	1	1	0	0
Hepatobiliary disorders					
Cholelithiasis	0	1	1	0	0
Hepatosplenomegaly	1	0	1	0	0
Infections and infestations					
Bacterial sepsis	0	0	0	1	0
Breast abscess	0	0	0	0	1
Breast cellulitis	0	0	0	0	1
Bronchiectasis	0	1	1	1	0
Bronchitis	0	1	1	0	0
Bronchopneumonia	1	0	1	0	0
Cellulitis	4	0	4	0	0
Clostridial infection	0	1	1	0	0
Diverticulitis	0	1	1	0	0

Table 72. Serious Adverse Events (All Causality) in Phase 3 Studies, 3 - 6 months

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Placebo	Adalimumab
Enterocolitis infectious	0	1	1	0	0
Gastroenteritis	1	0	1	0	0
Herpes zoster	2	0	2	0	0
Localised infection	1	0	1	0	0
Lower respiratory tract infection bacterial	0	1	1	0	0
Pyelonephritis	0	1	1	1	0
Pyelonephritis chronic	0	1	1	0	0
Sepsis	1	0	1	0	0
Injury, poisoning and procedural complications					
Fall	0	0	0	1	0
Foot fracture	1	1	2	0	0
Humerus fracture	2	0	2	0	0
Joint dislocation	1	0	1	0	0
Lower limb fracture	1	0	1	0	0
Multiple fractures	1	0	1	0	0
Patella fracture	1	0	1	0	0
Radius fracture	0	1	1	0	0
Spinal fracture	1	0	1	0	0
Subdural haematoma	0	1	1	0	0
Tendon rupture	0	1	1	0	0
Tibia fracture	1	0	1	0	0
Traumatic brain injury	1	0	1	0	0
Upper limb fracture	0	0	0	1	0
Metabolism and nutrition disorders					
Diabetes mellitus	0	2	2	0	0
Hyperkalaemia	0	1	1	0	0
Hyponatraemia	0	1	1	0	0
Musculoskeletal and connective tissue disorders					
Arthralgia	1	0	1	0	0
Back pain	1	0	1	0	0
Bone fistula	0	1	1	0	0
Foot deformity	0	1	1	0	0
Intervertebral disc protrusion	1	0	1	0	0
Osteonecrosis	1	0	1	0	0

Table 72. Serious Adverse Events (All Causality) in Phase 3 Studies, 3 - 6 months

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Placebo	Adalimumab
Rheumatoid arthritis	0	1	1	0	0
Spinal column stenosis	0	1	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Basal cell carcinoma	0	0	0	1	0
Breast cancer	0	1	1	0	0
Cervix carcinoma	0	1	1	0	0
Cholesteatoma	0	1	1	0	0
Metastatic squamous cell carcinoma	1	0	1	0	0
Non-small cell lung cancer	0	1	1	0	0
Ovarian granulosa-theca cell tumour	0	0	0	1	0
Salivary gland neoplasm	1	0	1	0	0
Nervous system disorders					
Amnesia	0	1	1	0	0
Cerebrovascular accident	2	0	2	0	0
Haemorrhage intracranial	1	0	1	0	0
Ischaemic stroke	0	0	0	1	0
Thalamic infarction	0	1	1	0	0
Transient ischaemic attack	2	0	2	0	0
Uraemic encephalopathy	0	0	0	1	0
Psychiatric disorders					
Mental disorder	1	0	1	0	0
Renal and urinary disorders					
Diabetic nephropathy	0	0	0	1	0
Hydronephrosis	0	0	0	1	0
Nephrolithiasis	1	0	1	0	0
Renal failure acute	0	1	1	1	0
Reproductive system and breast disorders					
Cervix disorder	1	0	1	0	0
Metrorrhagia	0	0	0	1	0
Ovarian cyst	0	0	0	1	0

Table 72. Serious Adverse Events (All Causality) in Phase 3 Studies, 3 - 6 months

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Placebo	Adalimumab
Ovarian torsion	1	0	1	0	0
Respiratory, thoracic and mediastinal disorders					
Aspiration	0	1	1	0	0
Chronic obstructive pulmonary disease	1	1	2	0	0
Interstitial lung disease	0	1	1	0	0
Pleural effusion	0	1	1	0	0
Pneumonia aspiration	1	0	1	0	0
Pulmonary embolism	0	2	2	0	0
Pulmonary fibrosis	0	1	1	0	0
Skin and subcutaneous tissue disorders					
Panniculitis	1	0	1	0	0
Vascular disorders					
Hypertensive crisis	1	0	1	0	0

Data as of 29 March 2011
Total number of patients with serious adverse events: 82.
A case is a single event or a series of related events not separated in time occurring in a single patient.
A case coded to several body systems may be counted as separate events and may include both serious and nonserious events.

Table 73. Serious Adverse Events (All Causality) in Phase 3 Studies, >6 months

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Adalimumab
Total preferred term events	*45*	*47*	***92***	*14*
Total number of cases	*44*	*38*	***82***	*12*
Total number of patients with serious adverse events	*42*	*35*	*77*	*12*
Blood and lymphatic system disorders				
Anaemia	0	1	1	0
Bone marrow failure	0	0	0	1

Table 73. Serious Adverse Events (All Causality) in Phase 3 Studies, >6 months

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Adalimumab
Thrombocytopenia	0	1	1	0
Cardiac disorders				
Angina unstable	0	1	1	0
Atrial fibrillation	0	1	1	0
Bundle branch block right	1	0	1	0
Cardiac failure congestive	0	1	1	0
Myocardial infarction	0	0	0	1
Endocrine disorders				
Autoimmune thyroiditis	1	0	1	0
Eye disorders				
Necrotising retinitis	0	1	1	0
Gastrointestinal disorders				
Abdominal hernia	0	0	0	1
Duodenal ulcer haemorrhage	1	0	1	0
Gastritis erosive	0	1	1	0
Haematemesis	0	1	1	1
Ileus	0	1	1	0
Inflammatory bowel disease	0	1	1	0
Melena	0	0	0	1
Peritonitis	0	1	1	0
Salivary gland enlargement	1	0	1	0
General disorders and administration site conditions				
Chest pain	2	3	5	1
Drug ineffective	0	1	1	0
Drug interaction	0	1	1	0
Hepatobiliary disorders				
Bile duct stone	1	0	1	0
Cholecystitis	2	0	2	0
Cholelithiasis	1	2	3	0
Infections and infestations				
Diverticulitis	0	1	1	0
Erysipelas	0	0	0	1
Gallbladder empyema	0	0	0	1
Gastroenteritis	0	1	1	0
Herpes zoster	1	0	1	0
Lung abscess	1	0	1	0
Pneumonia	6	2	8	0
Pneumonia cryptococcal	0	1	1	0

Table 73. Serious Adverse Events (All Causality) in Phase 3 Studies, >6 months

System Organ Class Preferred Term	**Tofacitinib 5 mg BID**	**Tofacitinib 10 mg BID**	**Tofacitinib All Doses**	**Adalimumab**
Pneumonia primary atypical	1	0	1	0
Pulmonary tuberculosis	0	4	4	0
Pyelonephritis acute	1	0	1	0
Salpingo-oophoritis	1	0	1	0
Septic shock	1	0	1	0
Urinary tract infection	0	1	1	0
Injury, poisoning and procedural complications				
Femur fracture	2	0	2	0
Fibula fracture	0	1	1	0
Joint dislocation	0	1	1	1
Lower limb fracture	1	0	1	0
Muscle injury	1	0	1	0
Spinal compression fracture	0	1	1	0
Tendon injury	1	0	1	0
Tendon rupture	1	0	1	0
Investigations				
Transaminases increased	1	0	1	0
Musculoskeletal and connective tissue disorders				
Bursitis	0	0	0	1
Cervical spinal stenosis	0	1	1	0
Fracture nonunion	1	0	1	0
Intervertebral disc protrusion	0	1	1	0
Lumbar spinal stenosis	0	1	1	0
Musculoskeletal chest pain	1	0	1	0
Osteoarthritis	2	0	2	0
Rheumatoid arthritis	2	0	2	1
Spondylolisthesis	0	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Breast cancer	0	1	1	0
Lung cancer metastatic	1	0	1	0
Lymphoma	0	1	1	0
Myelodysplastic syndrome	0	0	0	1
Neuroma	0	1	1	0
Non-small cell lung cancer	1	0	1	1

Table 73. Serious Adverse Events (All Causality) in Phase 3 Studies, >6 months

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Adalimumab
Nervous system disorders				
Headache	0	1	1	0
Sciatica	1	1	2	0
Syncope	0	1	1	0
Pregnancy, puerperium and perinatal conditions				
Abortion missed	0	1	1	0
Unintended pregnancy	0	1	1	0
Renal and urinary disorders				
Renal failure acute	0	1	1	0
Reproductive system and breast disorders				
Metrorrhagia	1	0	1	0
Respiratory, thoracic and mediastinal disorders				
Asthma	1	0	1	0
Interstitial lung disease	1	1	2	0
Pulmonary embolism	1	0	1	0
Pulmonary hypertension	0	1	1	0
Pulmonary sarcoidosis	1	0	1	0
Respiratory disorder	1	0	1	0
Respiratory failure	0	1	1	0
Skin and subcutaneous tissue disorders				
Skin ulcer	1	0	1	0
Vascular disorders				
Infarction	0	1	1	0

Data as of 29 March 2011
Total number of patients with serious adverse events: 89.
A case is a single event or a series of related events not separated in time occurring in a single patient.
A case coded to several body systems may be counted as separate events and may include both serious and nonserious events.

Table 74. Serious Adverse Events (All Causality) by System Organ Class and MedDRA Preferred Term in All Long-Term Extension Studies (All Patients): Number of Events

	Tofacitinib		
	5 mg BID n=1370	10 mg BID n=2145	All Doses n=3515
Total preferred term events	***412***	***299***	***711***
Total number of cases	***298***	***227***	***525***
Total number of patients with serious adverse events	***246***	***200***	***446***

Table 74. Serious Adverse Events (All Causality) by System Organ Class and MedDRA Preferred Term in All Long-Term Extension Studies (All Patients): Number of Events

	Tofacitinib		
	5 mg BID n=1370	10 mg BID n=2145	All Doses n=3515
System Organ Class Preferred Term			
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anaemia	4	1	5
Disseminated intravascular coagulation	1	0	1
Leukocytosis	1	0	1
Leukopenia	0	3	3
Pancytopenia	1	0	1
Thrombocytopenia	0	1	1
Thrombotic thrombocytopenic purpura	1	0	1
CARDIAC DISORDERS			
Acute coronary syndrome	1	0	1
Angina pectoris	2	0	2
Angina unstable	3	2	5
Arrhythmia	2	1	3
Atrial fibrillation	2	3	5
Atrial flutter	1	0	1
Bradycardia	1	0	1
Cardiac arrest	1	0	1
Cardiac failure	1	2	3
Cardiac failure congestive	1	2	3
Cardio-respiratory arrest	1	1	2
Coronary artery disease	1	2	3
Coronary artery stenosis	1	0	1
Coronary artery thrombosis	1	0	1
Long QT syndrome	0	1	1
Mitral valve incompetence	0	1	1
Myocardial infarction	3	1	4
Myocardial ischaemia	3	0	3
Pericardial effusion	0	1	1
Prinzmetal angina	1	0	1
Ventricular arrhythmia	1	0	1
Ventricular fibrillation	1	0	1
CONGENITAL, FAMILIAL AND GENETIC DISORDERS			
Atrial septal defect	0	1	1

Table 74. Serious Adverse Events (All Causality) by System Organ Class and MedDRA Preferred Term in All Long-Term Extension Studies (All Patients): Number of Events

	Tofacitinib		
	5 mg BID n=1370	10 mg BID n=2145	All Doses n=3515
EAR AND LABYRINTH DISORDERS			
Acute vestibular syndrome	1	0	1
Vertigo	2	1	3
Vertigo positional	2	0	2
ENDOCRINE DISORDERS			
Adrenal insufficiency	0	1	1
Goitre	0	1	1
Hyperthyroidism	0	1	1
EYE DISORDERS			
Cataract	1	2	3
Dacryostenosis acquired	1	0	1
Necrotising retinitis	1	0	1
Retinal artery occlusion	0	1	1
Retinitis	1	0	1
GASTROINTESTINAL DISORDERS			
Abdominal hernia	0	1	1
Abdominal pain	0	2	2
Abdominal pain upper	2	0	2
Abdominal strangulated hernia	1	0	1
Ascites	1	1	2
Colonic polyp	1	1	2
Diarrhoea	2	3	5
Diverticular perforation	1	2	3
Duodenal polyp	1	0	1
Duodenal ulcer haemorrhage	1	0	1
Enterocele	1	0	1
Gastric ulcer	1	0	1
Gastric ulcer haemorrhage	1	0	1
Gastritis	3	1	4
Gastritis erosive	1	0	1
Gastritis haemorrhagic	1	0	1
Gastrointestinal disorder	0	1	1
Haematochezia	1	0	1
Hiatus hernia	1	0	1
Ileus	1	1	2

Table 74. Serious Adverse Events (All Causality) by System Organ Class and MedDRA Preferred Term in All Long-Term Extension Studies (All Patients): Number of Events

	Tofacitinib		
	5 mg BID n=1370	10 mg BID n=2145	All Doses n=3515
Ileus paralytic	0	1	1
Inguinal hernia	2	2	4
Intestinal fistula	0	1	1
Intestinal perforation	1	0	1
Pancreatitis	2	2	4
Rectal haemorrhage	1	0	1
Reflux oesophagitis	2	0	2
Vomiting	1	0	1
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Asthenia	0	1	1
Chest discomfort	1	0	1
Chest pain	3	0	3
Death	1	0	1
Drug ineffective	2	0	2
Fatigue	0	1	1
Hernia	0	1	1
Multi-organ failure	1	0	1
Non-cardiac chest pain	1	0	1
Pyrexia	5	0	5
HEPATOBILIARY DISORDERS			
Autoimmune hepatitis	0	1	1
Cholecystitis	1	1	2
Cholecystitis acute	0	1	1
Cholecystitis chronic	1	1	2
Cholelithiasis	6	2	8
Hepatic congestion	0	1	1
Hepatic steatosis	1	0	1
Hepatotoxicity	1	0	1
Liver disorder	1	0	1
Sphincter of Oddi dysfunction	0	1	1
IMMUNE SYSTEM DISORDERS			
Allergy to arthropod bite	0	1	1
Anaphylactic reaction	1	0	1
Anaphylactic shock	1	0	1

Table 74. Serious Adverse Events (All Causality) by System Organ Class and MedDRA Preferred Term in All Long-Term Extension Studies (All Patients): Number of Events

	Tofacitinib		
	5 mg BID n=1370	10 mg BID n=2145	All Doses n=3515
INFECTIONS AND INFESTATIONS			
Abdominal abscess	1	0	1
Abscess	0	1	1
Abscess jaw	0	1	1
Abscess limb	1	2	3
Appendicitis	4	1	5
Arthritis bacterial	1	0	1
Bacteraemia	0	1	1
Bartholin's abscess	0	1	1
Bone tuberculosis	1	0	1
Bronchiolitis	1	0	1
Bronchitis	2	3	5
Bronchopneumonia	0	2	2
Bursitis infective	0	1	1
Cellulitis	3	4	7
Chronic tonsillitis	1	0	1
Clostridium difficile colitis	0	1	1
Cytomegalovirus hepatitis	1	0	1
Cytomegalovirus infection	1	0	1
Device related infection	2	0	2
Disseminated tuberculosis	2	0	2
Diverticulitis	5	1	6
Encephalitis viral	1	0	1
Enteritis infectious	1	1	2
Enterocolitis viral	1	0	1
Erysipelas	1	0	1
Extradural abscess	0	1	1
Gastroenteritis	3	4	7
Gastroenteritis viral	0	1	1
Gastrointestinal infection	0	1	1
Gastrointestinal viral infection	2	0	2
H1N1 influenza	0	1	1
Herpes dermatitis	1	0	1
Herpes simplex	0	1	1
Herpes virus infection	0	1	1

Table 74. Serious Adverse Events (All Causality) by System Organ Class and MedDRA Preferred Term in All Long-Term Extension Studies (All Patients): Number of Events

	Tofacitinib		
	5 mg BID n=1370	10 mg BID n=2145	All Doses n=3515
Herpes zoster	9	1	10
Infective spondylitis	0	1	1
Influenza	1	0	1
Lung infection	1	0	1
Meningitis	0	1	1
Meningitis cryptococcal	0	1	1
Mycobacterium avium complex infection	0	1	1
Necrotising fasciitis	1	0	1
Oesophageal candidiasis	1	1	2
Osteomyelitis	0	1	1
Periorbital cellulitis	0	1	1
Peritoneal infection	1	1	2
Pertussis	0	1	1
Pneumocystis jiroveci pneumonia	1	0	1
Pneumonia	12	17	29
Pneumonia haemophilus	2	0	2
Pneumonia legionella	0	1	1
Pneumonia mycoplasmal	1	0	1
Pneumonia pneumococcal	1	0	1
Pneumonia primary atypical	0	1	1
Pneumonia streptococcal	0	1	1
Postoperative abscess	0	2	2
Pulmonary tuberculosis	0	2	2
Purulent discharge	0	1	1
Pyelonephritis	3	1	4
Pyelonephritis acute	1	0	1
Respiratory tract infection	0	1	1
Salpingo-oophoritis	0	1	1
Secondary syphilis	1	0	1
Sepsis	3	0	3
Sepsis syndrome	0	1	1
Septic shock	1	3	4
Sinusitis	0	3	3
Sinusitis aspergillus	1	0	1
Sinusitis fungal	1	0	1

Table 74. Serious Adverse Events (All Causality) by System Organ Class and MedDRA Preferred Term in All Long-Term Extension Studies (All Patients): Number of Events

	Tofacitinib		
	5 mg BID n=1370	10 mg BID n=2145	All Doses n=3515
Staphylococcal bacteraemia	0	2	2
Staphylococcal infection	0	1	1
Streptococcal infection	1	0	1
Subcutaneous abscess	0	1	1
Tonsillitis	0	1	1
Tuberculosis	1	0	1
Tuberculosis of central nervous system	1	0	1
Upper respiratory tract infection	0	1	1
Urinary tract infection	6	2	8
Urosepsis	1	0	1
Viral infection	0	1	1
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Anastomotic ulcer	1	0	1
Ankle fracture	1	0	1
Burns second degree	0	1	1
Burns third degree	0	1	1
Cervical vertebral fracture	0	1	1
Compression fracture	1	1	2
Contusion	1	0	1
Fall	6	4	10
Femoral neck fracture	2	2	4
Femur fracture	2	6	8
Forearm fracture	1	0	1
Fracture	1	0	1
Fractured ischium	0	1	1
Hip fracture	2	1	3
Humerus fracture	1	1	2
Incorrect dose administered	1	0	1
Joint dislocation	2	0	2
Laceration	1	0	1
Lumbar vertebral fracture	1	0	1
Patella fracture	0	1	1
Procedural pain	0	1	1
Pubis fracture	1	0	1
Radius fracture	2	2	4

Table 74. Serious Adverse Events (All Causality) by System Organ Class and MedDRA Preferred Term in All Long-Term Extension Studies (All Patients): Number of Events

	Tofacitinib		
	5 mg BID n=1370	10 mg BID n=2145	All Doses n=3515
Rib fracture	0	1	1
Scapula fracture	1	0	1
Spinal compression fracture	0	1	1
Tendon rupture	5	3	8
Thoracic vertebral fracture	1	0	1
Tibia fracture	1	2	3
Ulna fracture	2	2	4
Wrist fracture	0	1	1
INVESTIGATIONS			
Alanine aminotransferase increased	1	0	1
Electrocardiogram T wave inversion	1	0	1
Liver function test abnormal	0	1	1
Metamyelocyte count increased	0	1	1
Myelocyte count increased	0	1	1
Transaminases increased	0	1	1
METABOLISM AND NUTRITION DISORDERS			
Decreased appetite	1	0	1
Dehydration	0	2	2
Diabetic ketoacidosis	0	1	1
Hypokalaemia	4	0	4
Hypovolaemia	1	0	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Arthralgia	1	2	3
Arthritis	1	1	2
Back pain	3	1	4
Cervical spinal stenosis	1	0	1
Connective tissue disorder	1	0	1
Extraskeletal ossification	0	1	1
Foot deformity	1	1	2
Groin pain	1	0	1
Haemarthrosis	1	0	1
Intervertebral disc disorder	0	1	1
Intervertebral disc protrusion	2	1	3
Joint destruction	1	0	1
Kyphosis	0	1	1

Table 74. Serious Adverse Events (All Causality) by System Organ Class and MedDRA Preferred Term in All Long-Term Extension Studies (All Patients): Number of Events

	Tofacitinib		
	5 mg BID n=1370	10 mg BID n=2145	All Doses n=3515
Ligament disorder	0	1	1
Lumbar spinal stenosis	1	2	3
Meniscal degeneration	1	0	1
Myopathy	1	0	1
Neck pain	1	0	1
Osteoarthritis	19	5	24
Osteonecrosis	3	1	4
Periostitis	1	0	1
Polyarthritis	1	0	1
Rheumatoid arthritis	4	2	6
Rotator cuff syndrome	1	0	1
Spinal column stenosis	3	2	5
Spondylitis	1	0	1
Spondylolisthesis	0	3	3
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
Basal cell carcinoma	1	2	3
Bladder cancer	0	1	1
Bladder neoplasm	1	0	1
Breast cancer	3	2	5
Breast cancer metastatic	1	0	1
Breast cancer stage II	1	0	1
Bronchial carcinoma	1	3	4
Central nervous system lymphoma	1	0	1
Cholesteatoma	1	0	1
Choroid plexus papilloma	1	0	1
Colon cancer	1	1	2
Endometrial cancer	1	0	1
Gallbladder cancer	1	0	1
Gastric cancer	3	1	4
Hepatic neoplasm malignant	0	1	1
Laryngeal cancer	1	0	1
Liposarcoma	1	0	1
Lung adenocarcinoma	0	1	1
Lung adenocarcinoma metastatic	0	1	1
Lung neoplasm	1	0	1

Table 74. Serious Adverse Events (All Causality) by System Organ Class and MedDRA Preferred Term in All Long-Term Extension Studies (All Patients): Number of Events

	Tofacitinib		
	5 mg BID n=1370	10 mg BID n=2145	All Doses n=3515
Lung neoplasm malignant	2	2	4
Lymphoproliferative disorder	1	0	1
Malignant ascites	1	0	1
Malignant melanoma	1	1	2
Malignant pleural effusion	1	0	1
Metastases to bone marrow	0	1	1
Metastases to liver	1	0	1
Metastases to lymph nodes	2	0	2
Omentum neoplasm	1	0	1
Ovarian cancer	2	0	2
Paget's disease of the breast	1	0	1
Prostate cancer	0	2	2
Prostate cancer metastatic	0	1	1
Renal cell carcinoma	0	1	1
Renal neoplasm	1	0	1
Salivary gland neoplasm	0	1	1
Small cell lung cancer metastatic	0	1	1
Small cell lung cancer stage unspecified	1	0	1
Squamous cell carcinoma	1	2	3
Synovial sarcoma	1	0	1
Thyroid cancer	1	0	1
Ureteric cancer	0	1	1
Uterine cancer	0	1	1
Uterine leiomyoma	1	0	1
Vulval cancer	1	0	1
NERVOUS SYSTEM DISORDERS			
Brain injury	1	0	1
Brain oedema	1	0	1
Carotid artery aneurysm	1	0	1
Carotid artery stenosis	0	1	1
Carpal tunnel syndrome	1	0	1
Cerebral haemorrhage	2	0	2
Cerebrovascular accident	1	3	4
Convulsion	2	0	2
Cubital tunnel syndrome	1	0	1

Table 74. Serious Adverse Events (All Causality) by System Organ Class and MedDRA Preferred Term in All Long-Term Extension Studies (All Patients): Number of Events

	Tofacitinib		
	5 mg BID n=1370	10 mg BID n=2145	All Doses n=3515
Facial nerve disorder	1	0	1
Headache	0	1	1
IIIrd nerve disorder	0	1	1
IIIrd nerve paralysis	1	0	1
Ischaemic stroke	1	0	1
Lacunar infarction	0	1	1
Loss of consciousness	2	0	2
Lumbar radiculopathy	1	0	1
Monoplegia	1	0	1
Nerve root compression	0	1	1
Neuritis	1	0	1
Radicular syndrome	0	1	1
Radiculitis	1	0	1
Sciatica	0	3	3
Sensory loss	0	1	1
Serotonin syndrome	0	1	1
Spinal claudication	0	2	2
Spinal cord compression	0	1	1
Syncope	1	1	2
Temporal lobe epilepsy	1	0	1
Transient global amnesia	1	0	1
Transient ischaemic attack	0	3	3
VIIth nerve paralysis	0	1	1
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS			
Abortion spontaneous	1	0	1
Unintended pregnancy	2	0	2
PSYCHIATRIC DISORDERS			
Alcoholism	0	1	1
Anxiety disorder	0	1	1
Completed suicide	1	1	2
Depression	0	1	1
Post-traumatic stress disorder	1	0	1
RENAL AND URINARY DISORDERS			
Calculus ureteric	1	0	1
Calculus urinary	1	0	1

Table 74. Serious Adverse Events (All Causality) by System Organ Class and MedDRA Preferred Term in All Long-Term Extension Studies (All Patients): Number of Events

	Tofacitinib		
	5 mg BID n=1370	10 mg BID n=2145	All Doses n=3515
Glomerulonephritis membranous	1	0	1
Haematuria	0	1	1
Nephrolithiasis	1	1	2
Pyelocaliectasis	1	0	1
Renal colic	0	1	1
Renal failure	3	1	4
Renal failure acute	4	1	5
Renal failure chronic	1	0	1
Renal impairment	0	1	1
Urinary incontinence	0	1	1
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Breast hyperplasia	1	0	1
Breast mass	1	0	1
Cervical dysplasia	0	1	1
Metrorrhagia	1	0	1
Ovarian cyst	1	1	2
Postmenopausal haemorrhage	1	0	1
Rectocele	0	1	1
Uterine polyp	1	0	1
Uterine prolapse	2	0	2
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Acute respiratory distress syndrome	0	2	2
Acute respiratory failure	1	0	1
Adenoidal hypertrophy	1	0	1
Bronchiectasis	0	1	1
Bronchospasm	1	0	1
Chronic obstructive pulmonary disease	2	2	4
Dyspnoea	3	1	4
Interstitial lung disease	1	1	2
Lung infiltration	0	1	1
Organising pneumonia	1	0	1
Pleural effusion	0	1	1
Pleurisy	1	0	1
Pneumothorax	0	1	1
Pulmonary embolism	1	1	2

Table 74. Serious Adverse Events (All Causality) by System Organ Class and MedDRA Preferred Term in All Long-Term Extension Studies (All Patients): Number of Events

	Tofacitinib		
	5 mg BID n=1370	10 mg BID n=2145	All Doses n=3515
Respiratory arrest	1	0	1
Respiratory distress	1	0	1
Respiratory failure	2	1	3
Rhinitis allergic	0	1	1
Sleep apnoea syndrome	0	1	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Drug rash with eosinophilia and systemic symptoms	1	0	1
Rash maculo-papular	1	0	1
Skin erosion	0	1	1
Skin ulcer	1	0	1
SURGICAL AND MEDICAL PROCEDURES			
Toe operation	0	1	1
VASCULAR DISORDERS			
Accelerated hypertension	1	0	1
Arteriosclerosis	2	0	2
Circulatory collapse	0	1	1
Deep vein thrombosis	6	3	9
Extremity necrosis	1	1	2
Haematoma	1	1	2
Hypertension	3	0	3
Hypertensive crisis	4	2	6
Hypovolaemic shock	0	1	1
Thrombophlebitis	1	0	1
Venous insufficiency	0	1	1
Venous thrombosis	1	0	1

Data as of 29 September 2011
BID=twice daily; pt-yr=patient-years.
A case is a single event or a series of related events not separated in time occurring in a single patient.
A case coded to several body systems may be counted as separate events and may include both serious and nonserious events.

14.4. Appendix IV: Discontinuations Due to Adverse Events Tables

Table 75. Adverse Events Leading to Discontinuation from Study in Phase 3 Studies, 0-3 Months

System Organ Class Preferred Term	**Tofacitinib** 5 mg BID N=1216 n (%)	**Tofacitinib** 10 mg BID N=1214 n (%)	**Tofacitinib** All Doses N=2430 n (%)	**Placebo** N=681 n (%)	**Adalimumab** N=204 n (%)
Total events	***75***	***64***	***139***	***25***	***10***
Blood and lymphatic system disorders	2 (0.2)	4 (0.3)	6 (0.2)	0	0
Anaemia	1 (0.1)	1 (0.1)	2 (0.1)	0	0
Iron deficiency anaemia	0	1 (0.1)	1	0	0
Lymphadenitis	1 (0.1)	0	1	0	0
Pancytopenia	0	1 (0.1)	1	0	0
Thrombocytopenia	0	1 (0.1)	1	0	0
Cardiac disorders	0	2 (0.2)	2 (0.1)	1 (0.1)	2 (1.0)
Acute myocardial infarction	0	0	0	0	1 (0.5)
Atrioventricular block complete	0	0	0	1 (0.1)	0
Cardiac arrest	0	0	0	0	1 (0.5)
Cardiac failure congestive	0	1 (0.1)	1	0	0
Myocardial infarction	0	1 (0.1)	1	0	0
Tachyarrhythmia	0	1 (0.1)	1	0	0
Ear and labyrinth disorders	1 (0.1)	3 (0.2)	4 (0.2)	0	0
Vertigo	1 (0.1)	3 (0.2)	4 (0.2)	0	0
Eye disorders	1 (0.1)	1 (0.1)	2 (0.1)	0	0
Dry eye	1 (0.1)	0	1	0	0
Ulcerative keratitis	0	1 (0.1)	1	0	0
Gastrointestinal disorders	8 (0.7)	7 (0.6)	15 (0.6)	5 (0.7)	2 (1.0)
Abdominal discomfort	0	0	0	1 (0.1)	0
Abdominal distension	0	1 (0.1)	1	0	0
Abdominal pain	1 (0.1)	0	1	0	0
Abdominal pain upper	3 (0.2)	0	3 (0.1)	0	0
Constipation	0	2 (0.2)	2 (0.1)	0	0
Diarrhoea	1 (0.1)	1 (0.1)	2 (0.1)	2 (0.3)	1 (0.5)

Table 75. Adverse Events Leading to Discontinuation from Study in Phase 3 Studies, 0-3 Months

System Organ Class Preferred Term	**Tofacitinib** 5 mg BID N=1216 n (%)	**Tofacitinib** 10 mg BID N=1214 n (%)	**Tofacitinib** All Doses N=2430 n (%)	**Placebo** N=681 n (%)	**Adalimumab** N=204 n (%)
Diverticular perforation	0	1 (0.1)	1	0	0
Dry mouth	1 (0.1)	0	1	0	0
Dyspepsia	2 (0.2)	0	2 (0.1)	1 (0.1)	1 (0.5)
Gastrointestinal pain	1 (0.1)	0	1	0	0
Glossodynia	0	0	0	1 (0.1)	0
Nausea	1 (0.1)	2 (0.2)	3 (0.1)	0	0
Tongue oedema	1 (0.1)	0	1	0	0
Vomiting	0	2 (0.2)	2 (0.1)	0	0
General disorders and administration site conditions	3 (0.2)	1 (0.1)	4 (0.2)	1 (0.1)	0
Chest pain	1 (0.1)	0	1	0	0
Drug ineffective	0	0	0	1 (0.1)	0
Face oedema	1 (0.1)	0	1	0	0
Oedema	0	1 (0.1)	1	0	0
Oedema peripheral	1 (0.1)	0	1	0	0
Hepatobiliary disorders	2 (0.2)	0	2 (0.1)	0	0
Cholecystitis	1 (0.1)	0	1	0	0
Hepatotoxicity	1 (0.1)	0	1	0	0
Immune system disorders	1 (0.1)	0	1	0	0
Drug hypersensitivity	1 (0.1)	0	1	0	0
Infections and infestations	12 (1.0)	14 (1.2)	26 (1.1)	0	0
Bronchitis	1 (0.1)	0	1	0	0
Bronchopneumonia	1 (0.1)	0	1	0	0
Cellulitis	2 (0.2)	0	2 (0.1)	0	0
Dengue fever	1 (0.1)	0	1	0	0
Diabetic foot infection	0	1 (0.1)	1	0	0
Diverticulitis	0	1 (0.1)	1	0	0
Herpes zoster	0	5 (0.4)	5 (0.2)	0	0
Herpes zoster disseminated	1 (0.1)	0	1	0	0
Influenza	0	1 (0.1)	1	0	0
Labyrinthitis	0	1 (0.1)	1	0	0
Liver abscess	0	1 (0.1)	1	0	0
Nasopharyngitis	1 (0.1)	0	1	0	0
Osteomyelitis	1 (0.1)	0	1	0	0

Table 75. Adverse Events Leading to Discontinuation from Study in Phase 3 Studies, 0-3 Months

System Organ Class Preferred Term	**Tofacitinib** 5 mg BID N=1216 n (%)	**Tofacitinib** 10 mg BID N=1214 n (%)	**Tofacitinib** All Doses N=2430 n (%)	**Placebo** N=681 n (%)	**Adalimumab** N=204 n (%)
Paronychia	1 (0.1)	0	1	0	0
Pneumocystis jiroveci pneumonia	1 (0.1)	0	1	0	0
Pneumonia	1 (0.1)	2 (0.2)	3 (0.1)	0	0
Pneumonia viral	1 (0.1)	0	1	0	0
Sialoadenitis	0	1 (0.1)	1	0	0
Skin infection	0	1 (0.1)	1	0	0
Tooth abscess	1 (0.1)	0	1	0	0
Upper respiratory tract infection	1 (0.1)	0	1	0	0
Urinary tract infection	0	2 (0.2)	2 (0.1)	0	0
Injury, poisoning and procedural complications	2 (0.2)	0	2 (0.1)	1 (0.1)	0
Femur fracture	1 (0.1)	0	1	0	0
Medication error	0	0	0	1 (0.1)	0
Overdose	1 (0.1)	0	1	0	0
Investigations	11 (0.9)	7 (0.6)	18 (0.7)	3 (0.4)	0
Alanine aminotransferase increased	2 (0.2)	1 (0.1)	3 (0.1)	0	0
Aspartate aminotransferase increased	1 (0.1)	1 (0.1)	2 (0.1)	0	0
Blood creatine phosphokinase increased	0	2 (0.2)	2 (0.1)	0	0
Blood creatinine increased	1 (0.1)	2 (0.2)	3 (0.1)	1 (0.1)	0
Blood pressure increased	1 (0.1)	0	1	0	0
Gamma-glutamyltransferase increased	0	1 (0.1)	1	0	0
Haemoglobin decreased	0	0	0	1 (0.1)	0
Hepatic enzyme increased	2 (0.2)	0	2 (0.1)	1 (0.1)	0
International normalised ratio increased	1 (0.1)	0	1	0	0
Liver function test abnormal	0	1 (0.1)	1	0	0

Table 75. Adverse Events Leading to Discontinuation from Study in Phase 3 Studies, 0-3 Months

System Organ Class Preferred Term	**Tofacitinib** 5 mg BID N=1216 n (%)	**Tofacitinib** 10 mg BID N=1214 n (%)	**Tofacitinib** All Doses N=2430 n (%)	**Placebo** N=681 n (%)	**Adalimumab** N=204 n (%)
Neutrophil count decreased	3 (0.2)	0	3 (0.1)	0	0
Platelet count decreased	1 (0.1)	0	1	0	0
Transaminases increased	1 (0.1)	0	1	1 (0.1)	0
White blood cell count decreased	3 (0.2)	0	3 (0.1)	0	0
Metabolism and nutrition disorders	0	2 (0.2)	2 (0.1)	2 (0.3)	0
Dehydration	0	2 (0.2)	2 (0.1)	1 (0.1)	0
Diabetes mellitus	0	0	0	1 (0.1)	0
Musculoskeletal and connective tissue disorders	3 (0.2)	4 (0.3)	7 (0.3)	8 (1.2)	1 (0.5)
Arthralgia	1 (0.1)	2 (0.2)	3 (0.1)	0	0
Back pain	1 (0.1)	0	1	0	0
Myalgia	1 (0.1)	0	1	1 (0.1)	0
Rheumatoid arthritis	0	0	0	7 (1.0)	1 (0.5)
Spinal column stenosis	0	1 (0.1)	1	0	0
Synovitis	0	1 (0.1)	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.2)	3 (0.2)	5 (0.2)	0	0
Breast cancer	0	1 (0.1)	1	0	0
Hair follicle tumour benign	1 (0.1)	0	1	0	0
Metastasis	0	1 (0.1)	1	0	0
Metastatic renal cell carcinoma	1 (0.1)	0	1	0	0
Squamous cell carcinoma of the cervix	0	1 (0.1)	1	0	0
Nervous system disorders	7 (0.6)	0	7 (0.3)	1 (0.1)	1 (0.5)
Carpal tunnel syndrome	0	0	0	0	1 (0.5)
Dizziness	1 (0.1)	0	1	1 (0.1)	0
Headache	5 (0.4)	0	5 (0.2)	0	0
Neuropathy peripheral	1 (0.1)	0	1	0	0

Table 75. Adverse Events Leading to Discontinuation from Study in Phase 3 Studies, 0-3 Months

System Organ Class Preferred Term	**Tofacitinib** 5 mg BID N=1216 n (%)	**Tofacitinib** 10 mg BID N=1214 n (%)	**Tofacitinib** All Doses N=2430 n (%)	**Placebo** N=681 n (%)	**Adalimumab** N=204 n (%)
Pregnancy, puerperium and perinatal conditions	0	0	0	1 (0.1)	0
Pregnancy	0	0	0	1 (0.1)	0
Psychiatric disorders	0	0	0	0	1 (0.5)
Anxiety	0	0	0	0	1 (0.5)
Renal and urinary disorders	0	1 (0.1)	1	1 (0.1)	1 (0.5)
Dysuria	0	1 (0.1)	1	0	0
Goodpasture's syndrome	0	0	0	1 (0.1)	0
IgA nephropathy	0	0	0	0	1 (0.5)
Reproductive system and breast disorders	1 (0.1)	1 (0.1)	2 (0.1)	0	0
Amenorrhoea	0	1 (0.1)	1	0	0
Breast engorgement	1 (0.1)	0	1	0	0
Vaginal discharge	1 (0.1)	0	1	0	0
Respiratory, thoracic and mediastinal disorders	3 (0.2)	2 (0.2)	5 (0.2)	0	0
Acute respiratory distress syndrome	1 (0.1)	0	1	0	0
Dry throat	1 (0.1)	0	1	0	0
Dyspnoea	1 (0.1)	2 (0.2)	3 (0.1)	0	0
Skin and subcutaneous tissue disorders	5 (0.4)	2 (0.2)	7 (0.3)	0	2 (1.0)
Alopecia	2 (0.2)	0	2 (0.1)	0	0
Angioedema	1 (0.1)	0	1	0	0
Dermatitis	0	1 (0.1)	1	0	0
Prurigo	1 (0.1)	0	1	0	0
Rash	1 (0.1)	1 (0.1)	2 (0.1)	0	2 (1.0)
Skin swelling	0	1 (0.1)	1	0	0
Vascular disorders	0	3 (0.2)	3 (0.1)	0	0
Aortic aneurysm	0	1 (0.1)	1	0	0
Hypertension	0	1 (0.1)	1	0	0
Venous thrombosis limb	0	1 (0.1)	1	0	0

Table 75. Adverse Events Leading to Discontinuation from Study in Phase 3 Studies, 0-3 Months

System Organ Class Preferred Term	Tofacitinib 5 mg BID N=1216 n (%)	Tofacitinib 10 mg BID N=1214 n (%)	Tofacitinib All Doses N=2430 n (%)	Placebo N=681 n (%)	Adalimumab N=204 n (%)

Adverse events are treatment emergent.
Note that percentages <0.1% are not displayed.
Except for the total number of adverse events, patients are counted only once per treatment in each row.

Table 76. Adverse Events Leading to Discontinuation from Study in Phase 3 Studies, 3 to 6 Months

System Organ Class Preferred Term	Tofacitinib 5 mg BID N=1451 n (%)	Tofacitinib 10 mg BID N=1439 n (%)	Tofacitinib All Doses N=2890 n (%)	Placebo N=221 n (%)	Adalimumab N=204 n (%)
Total events	***42***	***69***	***111***	***10***	***13***
Blood and lymphatic system disorders	3 (0.2)	1 (0.1)	4 (0.1)	0	1 (0.5)
Anaemia	1 (0.1)	1 (0.1)	2 (0.1)	0	0
Leukocytosis	1 (0.1)	0	1	0	0
Leukopenia	0	0	0	0	1 (0.5)
Thrombocytopenia	2 (0.1)	0	2 (0.1)	0	0
Cardiac disorders	1 (0.1)	2 (0.1)	3 (0.1)	1 (0.5)	0
Cardiac arrest	0	1 (0.1)	1	1 (0.5)	0
Cardiac failure congestive	0	1 (0.1)	1	0	0
Myocardial infarction	1 (0.1)	0	1	0	0
Pericarditis	0	1 (0.1)	1	0	0
Gastrointestinal disorders	3 (0.2)	8 (0.6)	11 (0.4)	0	1 (0.5)
Abdominal pain upper	0	1 (0.1)	1	0	0
Diarrhoea	0	1 (0.1)	1	0	0
Epigastric discomfort	0	1 (0.1)	1	0	0
Gastrointestinal haemorrhage	0	1 (0.1)	1	0	0
Glossodynia	0	1 (0.1)	1	0	0
Haematemesis	0	0	0	0	1 (0.5)
Haematochezia	0	0	0	0	1 (0.5)
Haemorrhoidal haemorrhage	1 (0.1)	0	1	0	0
Nausea	1 (0.1)	4 (0.3)	5 (0.2)	0	0
Pancreatitis	1 (0.1)	0	1	0	0
Vomiting	1 (0.1)	2 (0.1)	3 (0.1)	0	0

Table 76. Adverse Events Leading to Discontinuation from Study in Phase 3 Studies, 3 to 6 Months

System Organ Class Preferred Term	**Tofacitinib** 5 mg BID N=1451 n (%)	**Tofacitinib** 10 mg BID N=1439 n (%)	**Tofacitinib** All Doses N=2890 n (%)	**Placebo** N=221 n (%)	**Adalimumab** N=204 n (%)
General disorders and administration site conditions	0	2 (0.1)	2 (0.1)	0	0
Asthenia	0	1 (0.1)	1	0	0
General physical health deterioration	0	1 (0.1)	1	0	0
Multi-organ failure	0	1 (0.1)	1	0	0
Hepatobiliary disorders	2 (0.1)	0	2 (0.1)	0	0
Cholecystitis	1 (0.1)	0	1	0	0
Hepatosplenomegaly	1 (0.1)	0	1	0	0
Infections and infestations	13 (0.9)	9 (0.6)	22 (0.8)	2 (0.9)	4 (2.0)
Bacterial sepsis	0	0	0	1 (0.5)	0
Breast abscess	0	0	0	0	1 (0.5)
Bronchiectasis	0	0	0	1 (0.5)	0
Cellulitis	2 (0.1)	0	2 (0.1)	0	1 (0.5)
Diverticulitis	0	1 (0.1)	1	0	0
Enterocolitis bacterial	0	1 (0.1)	1	0	0
Erysipelas	0	0	0	0	1 (0.5)
Gallbladder empyema	0	0	0	0	1 (0.5)
Gastroenteritis	0	1 (0.1)	1	0	0
Genital herpes	0	1 (0.1)	1	0	0
Haematoma infection	1 (0.1)	0	1	0	0
Herpes zoster	2 (0.1)	0	2 (0.1)	0	0
Herpes zoster infection neurological	0	0	0	0	1 (0.5)
Oesophageal candidiasis	1 (0.1)	0	1	0	0
Pneumonia	0	1 (0.1)	1	0	0
Pneumonia primary atypical	1 (0.1)	0	1	0	0
Pulmonary tuberculosis	0	1 (0.1)	1	0	0
Pyelonephritis	0	1 (0.1)	1	1 (0.5)	0
Pyelonephritis acute	1 (0.1)	0	1	0	0
Sepsis	1 (0.1)	0	1	0	0
Septic shock	1 (0.1)	0	1	0	0
Sinusitis	0	1 (0.1)	1	0	0
Tuberculous pleurisy	0	1 (0.1)	1	0	0

Table 76. Adverse Events Leading to Discontinuation from Study in Phase 3 Studies, 3 to 6 Months

System Organ Class Preferred Term	**Tofacitinib** 5 mg BID N=1451 n (%)	**Tofacitinib** 10 mg BID N=1439 n (%)	**Tofacitinib** All Doses N=2890 n (%)	**Placebo** N=221 n (%)	**Adalimumab** N=204 n (%)
Upper respiratory tract infection	3 (0.2)	0	3 (0.1)	0	0
Urinary tract infection	0	1 (0.1)	1	0	0
Injury, poisoning and procedural complications	1 (0.1)	1 (0.1)	2 (0.1)	0	0
Spinal fracture	1 (0.1)	0	1	0	0
Subdural haematoma	0	1 (0.1)	1	0	0
Investigations	5 (0.3)	12 (0.8)	17 (0.6)	0	1 (0.5)
Alanine aminotransferase increased	0	4 (0.3)	4 (0.1)	0	0
Aspartate aminotransferase increased	0	4 (0.3)	4 (0.1)	0	0
Blood creatinine increased	0	2 (0.1)	2 (0.1)	0	0
Blood pressure increased	0	1 (0.1)	1	0	0
Gamma-glutamyltransferase increased	1 (0.1)	2 (0.1)	3 (0.1)	0	0
Haemoglobin decreased	0	1 (0.1)	1	0	0
Hepatic enzyme increased	1 (0.1)	1 (0.1)	2 (0.1)	0	1 (0.5)
Transaminases increased	1 (0.1)	0	1	0	0
Weight increased	2 (0.1)	1 (0.1)	3 (0.1)	0	0
White blood cell count decreased	0	2 (0.1)	2 (0.1)	0	0
Metabolism and nutrition disorders	1 (0.1)	2 (0.1)	3 (0.1)	0	0
Decreased appetite	1 (0.1)	0	1	0	0
Diabetes mellitus	0	1 (0.1)	1	0	0
Hyperkalaemia	0	1 (0.1)	1	0	0
Musculoskeletal and connective tissue disorders	1 (0.1)	4 (0.3)	5 (0.2)	1 (0.5)	1 (0.5)
Intervertebral disc protrusion	0	1 (0.1)	1	0	0
Lupus-like syndrome	0	1 (0.1)	1	0	0
Myalgia	0	1 (0.1)	1	0	0
Rheumatoid arthritis	1 (0.1)	0	1	1 (0.5)	0

Table 76. Adverse Events Leading to Discontinuation from Study in Phase 3 Studies, 3 to 6 Months

System Organ Class Preferred Term	**Tofacitinib** 5 mg BID N=1451 n (%)	**Tofacitinib** 10 mg BID N=1439 n (%)	**Tofacitinib** All Doses N=2890 n (%)	**Placebo** N=221 n (%)	**Adalimumab** N=204 n (%)
Spinal osteoarthritis	0	1 (0.1)	1	0	0
Spondylolisthesis	0	0	0	0	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1)	3 (0.2)	4 (0.1)	1 (0.5)	1 (0.5)
Basal cell carcinoma	0	0	0	1 (0.5)	0
Cervix carcinoma	0	1 (0.1)	1	0	0
Lymphoma	0	1 (0.1)	1	0	0
Metastatic squamous cell carcinoma	1 (0.1)	0	1	0	0
Myelodysplastic syndrome	0	0	0	0	1 (0.5)
Non-small cell lung cancer	0	1 (0.1)	1	0	0
Nervous system disorders	1 (0.1)	3 (0.2)	4 (0.1)	1 (0.5)	0
Hypoaesthesia	0	1 (0.1)	1	0	0
Lacunar infarction	0	1 (0.1)	1	0	0
Somnolence	0	1 (0.1)	1	0	0
Syncope	0	1 (0.1)	1	0	0
Tremor	1 (0.1)	0	1	0	0
Uraemic encephalopathy	0	0	0	1 (0.5)	0
Pregnancy, puerperium and perinatal conditions	1 (0.1)	1 (0.1)	2 (0.1)	0	0
Pregnancy	1 (0.1)	0	1	0	0
Unintended pregnancy	0	1 (0.1)	1	0	0
Psychiatric disorders	1 (0.1)	0	1	0	0
Mental disorder	1 (0.1)	0	1	0	0
Renal and urinary disorders	0	2 (0.1)	2 (0.1)	1 (0.5)	0
Diabetic nephropathy	0	0	0	1 (0.5)	0
Hydronephrosis	0	0	0	1 (0.5)	0
Renal failure	0	1 (0.1)	1	0	0
Renal failure acute	0	1 (0.1)	1	1 (0.5)	0
Respiratory, thoracic and mediastinal disorders	1 (0.1)	4 (0.3)	5 (0.2)	0	0
Dyspnoea	0	1 (0.1)	1	0	0

Table 76. Adverse Events Leading to Discontinuation from Study in Phase 3 Studies, 3 to 6 Months

System Organ Class Preferred Term	**Tofacitinib** 5 mg BID N=1451 n (%)	**Tofacitinib** 10 mg BID N=1439 n (%)	**Tofacitinib** All Doses N=2890 n (%)	**Placebo** N=221 n (%)	**Adalimumab** N=204 n (%)
Pneumonia aspiration	1 (0.1)	0	1	0	0
Pulmonary embolism	0	2 (0.1)	2 (0.1)	0	0
Pulmonary fibrosis	0	1 (0.1)	1	0	0
Skin and subcutaneous tissue disorders	5 (0.3)	1 (0.1)	6 (0.2)	0	1 (0.5)
Decubitus ulcer	1 (0.1)	0	1	0	0
Dermatitis allergic	1 (0.1)	0	1	0	0
Drug eruption	1 (0.1)	0	1	0	0
Panniculitis	1 (0.1)	0	1	0	0
Pruritus	0	0	0	0	1 (0.5)
Rash erythematous	0	1 (0.1)	1	0	0
Rash generalized	0	0	0	0	1 (0.5)
Rash vesicular	1 (0.1)	0	1	0	0
Vascular disorders	0	1 (0.1)	1	0	0
Infarction	0	1 (0.1)	1	0	0

Adverse events are treatment emergent.
Note that percentages <0.1% are not displayed.
Except for the total number of adverse events, patients are counted only once per treatment in each row.

Table 77. Adverse Events Leading to Discontinuation from Study in Phase 3 Studies, >6 Months

System Organ Class Preferred Term	**Tofacitinib** 5 mg BID N=1056 n (%)	**Tofacitinib** 10 mg BID N=1046 n (%)	**Tofacitinib** All Doses N=2102 n (%)	**Adalimumab** N=204 n (%)
Total events	***21***	*30*	***51***	*5*
Blood and lymphatic system disorders	1 (0.1)	1(0.1)	2 (0.1)	0
Anaemia	1 (0.1)	0	1	0
Thrombocytopenia	0	1 (0.1)	1	0
Cardiac disorders	0	1 (0.1)	1	0
Cardiac failure congestive	0	1 (0.1)	1	0
Eye disorders	0	1 (0.1)	1	0
Necrotising retinitis	0	1 (0.1)	1	0
Gastrointestinal disorders	1 (0.1)	3 (0.3)	4 (0.2)	0
Diarrhoea	1 (0.1)	0	1	0
Enteritis	0	1 (0.1)	1	0
Ileus	0	1 (0.1)	1	0

Table 77. Adverse Events Leading to Discontinuation from Study in Phase 3 Studies, >6 Months

System Organ Class Preferred Term	**Tofacitinib** 5 mg BID N=1056 n (%)	**Tofacitinib** 10 mg BID N=1046 n (%)	**Tofacitinib** All Doses N=2102 n (%)	**Adalimumab** N=204 n (%)
Mouth ulceration	1 (0.1)	0	1	0
Peritonitis	0	1 (0.1)	1	0
General disorders and administration site conditions	1 (0.1)	1 (0.1)	2 (0.1)	1 (0.5)
Fatigue	0	0	0	1 (0.5)
Pyrexia	1 (0.1)	1 (0.1)	2 (0.1)	0
Infections and infestations	5 (0.5)	10 (1.0)	15 (0.7)	0
Aspergilloma	0	1 (0.1)	1	0
Bronchopneumonia	0	1 (0.1)	1	0
Diverticulitis	0	1 (0.1)	1	0
Herpes zoster	1 (0.1)	2 (0.2)	3 (0.1)	0
Lung abscess	1 (0.1)	0	1	0
Lymph node tuberculosis	0	1 (0.1)	1	0
Pneumonia	2 (0.2)	1 (0.1)	3 (0.1)	0
Pneumonia cryptococcal	0	1 (0.1)	1	0
Pulmonary tuberculosis	0	2 (0.2)	2 (0.1)	0
Salpingo-oophoritis	1 (0.1)	0	1	0
Injury, poisoning and procedural complications	1 (0.1)	0	1	0
Ankle fracture	1 (0.1)	0	1	0
Investigations	2 (0.2)	5 (0.5)	7 (0.3)	0
Alanine aminotransferase increased	1 (0.1)	1 (0.1)	2 (0.1)	0
Aspartate aminotransferase increased	1 (0.1)	1 (0.1)	2 (0.1)	0
Blood alkaline phosphatase increased	0	1 (0.1)	1	0
Blood creatinine increased	1 (0.1)	3 (0.3)	4 (0.2)	0
Gamma-glutamyltransferase increased	0	1 (0.1)	1	0
Lymphocyte count decreased	0	1 (0.1)	1	0
Musculoskeletal and connective tissue disorders	2 (0.2)	0	2 (0.1)	2 (1.0)

Table 77. Adverse Events Leading to Discontinuation from Study in Phase 3 Studies, >6 Months

System Organ Class Preferred Term	**Tofacitinib** 5 mg BID N=1056 n (%)	**Tofacitinib** 10 mg BID N=1046 n (%)	**Tofacitinib** All Doses N=2102 n (%)	**Adalimumab** N=204 n (%)
Rheumatoid arthritis	2 (0.2)	0	2 (0.1)	2 (1.0)
Tensynovitis	0	0	0	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.2)	1 (0.1)	3 (0.1)	1 (0.5)
Breast cancer	0	1 (0.1)	1	0
Lung cancer metastatic	1 (0.1)	0	1	0
Non-small cell lung cancer	1 (0.1)	0	1	1 (0.5)
Nervous system disorders	0	1 (0.1)	1	0
Headache	0	1 (0.1)	1	0
Renal and urinary disorders	0	1 (0.1)	1	0
Nephrolithiasis	0	1 (0.1)	1	0
Renal failure acute	0	1 (0.1)	1	0
Respiratory, thoracic and mediastinal disorders	1 (0.1)	1 (0.1)	2 (0.1)	0
Interstitial lung disease	1 (0.1)	1 (0.1)	2 (0.1)	0
Skin and subcutaneous tissue disorders	2 (0.2)	0	2 (0.1)	0
Blister	1 (0.1)	0	1	0
Skin lesion	1 (0.1)	0	1	0
Skin ulcer	1 (0.1)	0	1	0

Adverse events are treatment emergent.
Note that percentages <0.1% are not displayed.
Except for the total number of adverse events, patients are counted only once per treatment in each row.

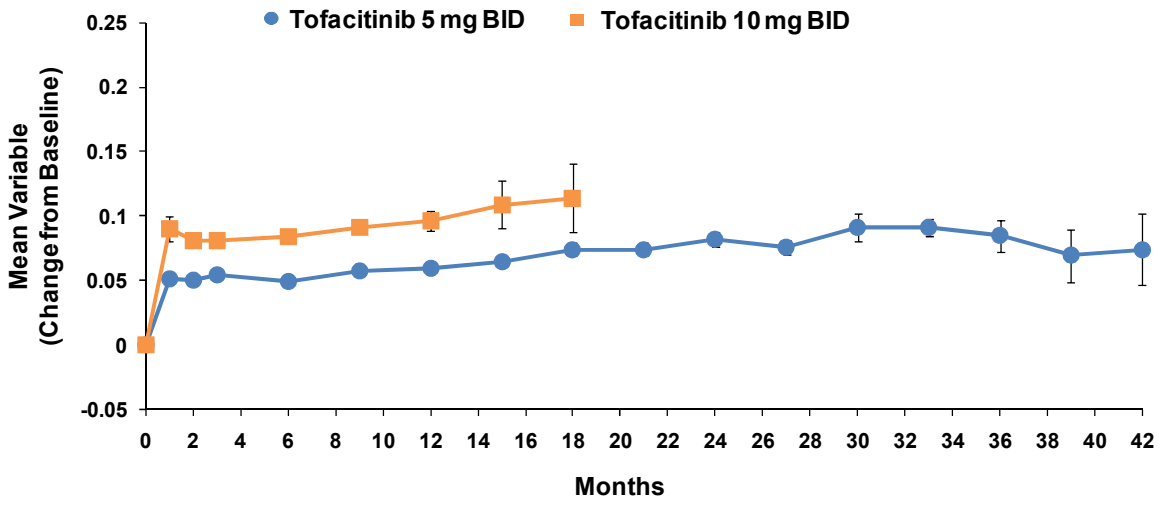
Table 78. Adverse Events Leading to Discontinuation from Study for Long-Term Extension Studies

	Tofacitinib		
System Organ Class	**5 mg BID**	**10 mg BID**	**All Doses**
	N=1370 n (%)	**N=2145** n (%)	**N=3515** n (%)
Total patients with AEs leading to discontinuation	***173 (12.6)***	***145 (6.8)***	***318 (9.0)***
Total preferred term events	***233***	***179***	***412***
Total pt-yr of drug exposure	***2725.8***	***1683.8***	***4409.7***
Blood and lymphatic system disorders	6 (0.4)	4 (0.2)	10 (0.3)
Cardiac disorders	11 (0.8)	3 (0.1)	14 (0.4)
Ear and labyrinth disorders	1 (0.1)	1	2 (0.1)
Eye disorders	2 (0.1)	1	3 (0.1)
Gastrointestinal disorders	16 (1.2)	6 (0.3)	22 (0.6)
General disorders and administration site conditions	5 (0.4)	2 (0.1)	7 (0.2)
Hepatobiliary disorders	6 (0.4)	2 (0.1)	8 (0.2)
Immune system disorders	0	1	1
Infections and infestations	54 (3.9)	63 (2.9)	117 (3.3)
Injury, poisoning and procedural complications	5 (0.4)	4 (0.2)	9 (0.3)
Investigations	27 (2.0)	26 (1.2)	53 (1.5)
Metabolism and nutrition disorders	0	2 (0.1)	2 (0.1)
Musculoskeletal and connective tissue disorders	7 (0.5)	5 (0.2)	12 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	32 (2.3)	16 (0.7)	48 (1.4)
Nervous system disorders	11 (0.8)	5 (0.2)	16 (0.5)
Pregnancy, puerperium and perinatal conditions	1 (0.1)	0	1
Psychiatric disorders	0	1	1
Renal and urinary disorders	5 (0.4)	0	5 (0.1)
Reproductive system and breast disorders	1 (0.1)	1	2 (0.1)
Respiratory, thoracic and mediastinal disorders	6 (0.4)	11 (0.5)	17 (0.5)
Skin and subcutaneous tissue disorders	5 (0.4)	6 (0.3)	11 (0.3)
Vascular disorders	2 (0.1)	4 (0.2)	6 (0.2)

BID=twice daily; pt-yr=patient-years.
Note that percentages <0.1% are not displayed.
Except for the total number of adverse events, patients are counted only once per treatment in each row.
Percentages for gender-specific events use the corresponding gender count as a denominator.

14.5. Appendix V: Serum Creatinine

Figure 65. Mean (±SE) Change From Baseline* in Serum Creatinine (mg/dL) in Long-Term Extension Studies (All Patients)



BID=twice daily; SE=standard error
* Baseline for the LTE studies was defined as the baseline visit of the index study for those patients who enrolled in the LTE study within 14 days of completing the index study (which included most patients), and as the last pre-drug visit of the LTE study for those patients who enrolled in the LTE study more than 14 days after completing the index study.